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JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY SEPTEMBER 18 1954

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 18 1954

THE PHYSIOLOGY OF THE THYMUS GLAND*

BY

GEOFFREY KEYNES, M.D., F.R.C.P., F.R.C.S., F.R.C.O.G.

Consulting Surgeon, St. Bartholomew's Hospital, London

Thomas Young, whom we are commemorating, entered on his medical career in 1793 at the age of 20 as a student at my own hospital of St. Bartholomew. He published his first scientific paper on the accommodating power of the eye very soon afterwards, and in the next year, 1794, was elected a Fellow of the Royal Society. It may be doubted whether it would now be possible for any medical student, however brilliant, to achieve an F.R.S. in his first year at hospital. The Royal Society, however, took a chance on Thomas Young, and seldom has their choice been more fully justified in the event. I need not enlarge on Young's outstanding achievements in his work on the physiology and physics of the eye. Much of his work has stood the test of time, and his teaching is current at the present day. He was, moreover, a man of extraordinary versatility, so that he became eminent as physiologist, mathematician, physicist, physician to St. George's Hospital, and, unexpectedly, Egyptologist. He was, indeed, the chief interpreter of the Rosetta Stone. He also made observations on the habits of spiders.

All these positive achievements contrast richly with the comparative poverty of the theme I am proposing to unfold under the aegis of Young's name. If a student were asked to-day, "What is known of the physiology of the thymus gland," he would probably return the perfectly reasonable answer, "Well, practically nothing." So it is a sort of spider's web story that I shall have to spin, full of holes and very shaky. Fortunately the term "physiology" does not compel nowadays confinement within a single scientific cell. No compartments are now watertight, and none will mind, I hope, if I touch on matters that are anatomical, clinical, pathological, and historical. I have even seen the term "physio-pathology" used recently in a reputable journal, and this gives me a little more confidence.

The Harveian Orator for 1953 has also given encouragement—"The advances in physiology," Dr. Graham said, "have been made not only by those who work in the physiological laboratories but also by the whole army of clinicians, chemists, biochemists, biologists, physicists, anatomists, pharmacologists, and pathologists who have contributed their experiences." Why did not he add "surgeons" to his list? But it is not unusual to find that surgeons are regarded merely as carpenters or plumbers, and not very intelligent ones either. Call us "craftsmen" and we shall not mind.

*The Thomas Young Memorial Lecture, delivered at St. George's Hospital, April 2, 1954.

First Recognition of the Thymus

Thomas Young, the Egyptologist, was born too soon to have known of the remarkable medical papyri that have come to light in more recent times. It is now evident that the Egyptians through their practice of embalmment became familiar with the internal anatomy and the diseases both of men and of animals at least a millennium before any other people. There can be little doubt that the thymus gland was noticed and possibly described in the Valley of the Nile 1,500 years before Christ. But much of this early knowledge was not disseminated, and the thymus gland was probably unknown to Hippocrates and Aristotle. It was, indeed, first mentioned by Rufus the Ephesian in the course of enumerating the anatomical discoveries made at the School of Alexandria under the Ptolemies—that is, about the first century B.C. A function was first assigned to the thymus by Galen, in the second century A.D.: he, seeing the gland sitting like a firm cushion in the anterior mediastinum, suggested that it was put there to protect the vena cava from coming into contact with the hard surface of the sternum. Even the great Vesalius, thirteen centuries later, was unable to improve on this, and it was not until the middle of the seventeenth century that Glisson, understanding more of its structure and anatomy than his predecessors, suggested that it might be somehow connected with the growth of the foetus. It is certainly a massive-looking object in the foetus and infant.

The first important monograph on the thymus was published by Sir Astley Cooper in 1832. This, like all Cooper's books, is an admirable piece of work. He investigated in detail the thymus glands of the calf and of the human foetus. In both of these he was impressed by the amount of milky fluid that the gland seemed to contain, and in both he described and injected with wax numerous cavities, which he thought were lined with a smooth membrane. It is possible, however, that he was not correct in this. It is notorious that the thymus disintegrates very quickly after death, and Cooper's cavities were probably artifacts due to the breakdown of the pulpy lymphoid tissue of which the gland is largely composed. I am not familiar with the fresh glands of calves, but I can certify that the freshly removed human thymus, even in very young children, is almost entirely solid.

Sir Astley Cooper demonstrated that the thymus is a conglomeration of small lobules, as can be readily seen in a stained section, and he rejoiced in "unravelling"

the gland until he obtained long ropes of lobules, which he likened to a necklace of beads. He traced the development of the thymus in the human foetus, and gave admirable figures of it at different stages. He dissected it with great care, determining that its blood supply was derived from the internal mammary and inferior thyroid arteries. He also observed, quite correctly, that the thymic veins drain mainly into the left innominate vein, though he did not record the fact that the veins from the two lobes commonly unite to form one large vessel ending in the innominate. Of the physiology of the thymus he wrote: "That an important function must be performed by an organ as uniformly found, of a size so large, of a highly vascular structure and secreting abundantly, no one who duly considers the subject can for a moment hesitate to acknowledge, and for myself I cannot subscribe to the opinion of those who think this Gland is designed merely to fill a space which the lungs in their expanded state after the birth of the foetus may be destined to occupy in respiration." He concluded that the function of the thymus is evidently connected with the foetal stages of existence, since it afterwards gradually lessens in size, and that it secretes a fluid suitable for promoting the growth of the foetus.

We must, I think, agree with Sir Astley that so large and conspicuous an organ cannot have been formed without serious purpose, and we can now add the fact established by comparative anatomists that the thymus is present in all chordate animals—that is, in all mammals, birds, reptiles, and fishes. It has even been reported as present in amphioxus, the most primitive chordate of all. Can we, however, still subscribe to his suggestion that its function is to promote growth in the foetus? It seems likely that this view is all too simple, and I shall presently come to the consideration of other possibilities.

Size of the Thymus

There is a widespread belief that the thymus atrophies and disappears in adult life, and it is indeed virtually unknown to the student working on dissecting-room bodies. This belief has probably persisted from the time of Galen, who noted its involution in post-foetal life. On the other hand, Glisson in 1650 stated that it frequently persisted for considerable periods after birth. In 1820 Meckel maintained that it increased proportionately to increase of body weight for the first one or two years, but that it had disappeared by the twelfth year. In 1877 Sappey held that it persisted through life, and in 1890 Waldeyer supplemented this with the statement that a fatty mass of the shape of the original gland and in the same position, containing remnants of active gland tissue, could still be found late in life. At last we are getting somewhere near the truth.

In 1906 Hammar published a careful analysis of the size of the thymus in 126 individuals, of whom 55 were under 15 years of age. His conclusion was that the gland was proportionately greatest at birth—in proportion, that is, to the weight of the body—but that it steadily decreased in relative size afterwards. Nevertheless its absolute weight is greatest at puberty (Hoskins, 1918)—a very different thing from the earlier statement that it disappeared by the age of 12.

The investigation was taken a stage further in 1925 by Bratton, who investigated the size of the thymus in 337 individuals under 16 years of age who had died from acute medical or surgical conditions, thus eliminating so far as possible changes due to pathological processes in other parts of the body. Bratton's conclusions were that the absolute weight of the thymus increases rapidly in the first two years of life, then changes little till the seventh year; thereafter it again increases, but falls slightly after the age of 11. He also found a sex difference, the gland being heavier at birth in the male, though the female wins after the age of 11.

It seems to be extraordinarily difficult to get at the truth concerning even the size of this enigmatic organ, apart from the still more difficult question of its function. It may therefore be worth adding my own testimony, derived from the surgical removal of the thymus from over 250 patients suffering from myasthenia gravis of ages ranging from 2½ to 60. The two lobes of the thymus can always be identified and cleanly dissected at any age. Its size varies at all ages within very wide limits, weights having been found in my series of adults from 2.7 g. to 32 g. The average weight is from 12 to 15 g. In older people the gland tends to weigh less in relation to its size, as it is often partly or largely replaced by fat.

Let us, therefore, once and for all discard the belief that the thymus is a disappearing organ. Variable it certainly is, but it is always there, and usually of considerable size. The fact that it is not seen in dissecting-room bodies is easily explained. In the first place, the bodies are usually those of old people; secondly, the thymus shrinks greatly during the process of preservation and no doubt disintegrates too; and, thirdly, there is much post-mortem evidence to show that shrinkage of the gland, or atrophy, or involution, or whatever you like to call it, accompanies all wasting diseases, starvation, and overwork. It has long been known to butchers that animals driven or worked to excess have smaller sweetbreads (as they call both thymus and pancreas, and perhaps thyroid too) than those that have been treated with more consideration. The thymus is, then, highly sensitive to conditions affecting the body as a whole, though usually in the direction of shrinkage rather than of hypertrophy.

"Status Lymphaticus"

There is, however, or rather *was*, a condition, much talked of in the past, in which the thymus was supposed to be greatly enlarged. This was called "status lymphaticus," and it was supposed to be responsible for many deaths under anaesthetics, and even for sudden deaths of young people in the absence of any other contributory factor. It was a great standby for coroners when clearly no blame could be laid upon the unfortunate anaesthetists. Everyone was satisfied with a verdict of status lymphaticus, even including the relatives of the deceased, the term being known to the laity as well as to the doctors. There is much comfort to be derived from the application of a familiar label, even though it is really no more than a confession of ignorance. But eventually so prevalent did this mysterious disease become that a committee of investigation was formed by the Medical Research Council, their report being published by Young and Turnbull in 1931. This very competent committee based its findings on an analysis of 680 necropsies made after sudden death from any cause. It was established that the normal thymus is much larger than was generally supposed. It may weigh as much as 70 or 80 g. up to the age of 16 years. If the weight of the thymus be correlated with the body weight and stature, then a boy of 6 weighing 19 kg. and 104 cm. in height would have an average thymic weight of 28.3 g. Of all individuals of this age 17% would have a thymus exceeding 40 g. and 4% exceeding 50 g.

Age	Weight of Thymus	Cause of Death
32	35·5 g.	Anaesthesia or shock
25	73·0 „	„ „ „
39	37·0 „	Coal-gas poisoning
57	31·0 „	„ „ „
24	47·0 „	Fractured skull
46	39·0 „	Laceration of brain
17	47·5 „	Crushed chest and haemothorax
28	35·0 „	Multiple injuries
55	49·3 „	Hanging
70	28·0 „	Infarction of heart

As further evidence of the surprisingly large size of the normal thymus Young and Turnbull give details (see Table) of a few selected individuals. It will be noticed that people aged 55, 57, and 70 had glands weighing 49, 31, and 28 g. In only two of these people had death been attributed to anaesthesia or shock. One patient of 25 had a very large thymus, weighing 73 g., but in an analysis of 23 other

instances in which death was attributed to anaesthesia or shock there was no significant deviation from the average weight of the thymus in the various age groups of the patients. In one in which death was definitely stated to be due to status lymphaticus the thymus was not significantly enlarged. In most instances other adequate explanations of sudden death were found, such as inhalation of blood after tonsillectomy, purulent bronchitis, and so forth.

The committee also found that there was no significant relation between the size of the thymus and the amount of other lymphoid structures, with the possible exception of the lingual tonsil. This observation was important, because it was popularly believed that in status lymphaticus there was a general hypertrophy of all the lymphoid structures of the body. The committee concluded that the facts elicited by their inquiry were in harmony with those of other observers in affording no evidence that so-called status thymolymphaticus (to give it its full title) has any existence at all as a pathological entity.

Additional evidence is to be found in a paper by Werne and Garrow (1953). These observers made a full examination of a large number of infants who had died suddenly when apparently in good health, either having been found dead or having been actually observed to die. The gross necropsy evidence was inconclusive, but microscopical evidence showed that fulminating respiratory disease was present in every single one.

It seems to be clear that supposed evidence of status thymolymphaticus is in reality based on a widespread ignorance of the true facts concerning the normal thymus, coupled with too frequent reliance on macroscopic appearances in performing post-mortem examinations. Nevertheless old beliefs die very hard, and the subject reappears regularly in the columns of the medical journals. A recent correspondence in the *British Medical Journal* has been true to type, with evidence derived from a single example or based on the impression received by an individual (this time the late Sir Bernard Spilsbury) who had not actually recorded any evidence at all. It would seem to be better to read the full and careful evidence collected by the Turnbull committee than to try to resurrect a medical chimera which has really been dead for more than 20 years.

Mention must be made of the theory of thyro-thymic function advanced by the late George Scott Williamson (1925–6) and by Dr. Innes Pearce. These observers, after prolonged research into the function of the thyroid gland and its intimate anatomy, announced their belief that there was anatomical continuity between the lymphatic systems of the two glands, and that the thymus formed a reservoir for thyroid products. But their theory postulated that the thyroid has a "major function" (its nature undetermined) as well as an endocrine one. Their observations have not been confirmed, and, so far as I know, no further work has been done on the same lines, so that the question of a possible thyro-thymic condominium has not been resolved.

Relation to the "Endocrine Orchestra"

The thymus, being a ductless gland in the sense that it has no duct, whether or no there is any active secretion, has naturally not escaped the notice of the investigators of the endocrine organs. I have silently passed over the innumerable researches carried out during the last 75 years in the attempt to discover a function for the thymus. Most of these were affected by the assumption, already mentioned, that the organ had some influence on growth, either pre- or post-natal. Extracts have been made and injected into young animals. Thymus glands have been removed in the hope that the thymectomized animals would fail to grow. I am sure that the serum of thymectomized goats must at one time or another have been used experimentally to prove or disprove a theory. This animal has always been a favourite victim of the physiologists. But all was in vain. No extract given in excess or any deprivation was ever shown to have any effect at all. The thymus kept its secret. More recently, however, the endocrinologists have evolved more subtle methods of research, and these have proved more fertile. It seems fair to assume that the thymus, in spite of its hypocritical silence, is in reality a member of the endocrine orchestra—a term invented, I believe, by the late Sir Walter Langdon-Brown. Very well, then; let us investigate the relation of the thymus to the other instruments in the orchestra.

To begin with, there is the fact that the thymus is frequently enlarged in patients with primary toxic goitres (a fact duly noted by Sir Astley Cooper in 1832), and this enlargement is apt to be associated with lymphoid hypertrophy in general, affecting the tonsils and indeed the whole pharyngeal circle of lymphoid tissue, and the lymph nodes of the body. The thyroid gland itself may, of course, also show a striking infiltration with lymphocytes. Since toxic goitre is usually one of the wasting diseases, this thymic hypertrophy seems to be somewhat contradictory, but it has so far only been observed and not explained—unless it is to be related to the fact, observed by Rawson *et al.* (1942, 1943), that thyrotrophic hormone is neutralized by the tissues of the thyroid gland, thymus gland, and lymph nodes, a faculty shared by no other structure in the body. Attention may then be turned to the sex glands. It is found that castration prevents, or delays, the normal involution of the thymus after the age of puberty. Conversely, administration of androgens causes premature involution of the thymus in animals before the age of puberty. I have not seen any record of the effect of oestrogens.

Now, what of the effects exerted by the adrenal and the anterior pituitary? Here there is something definite to relate. Adrenal hypertrophy and thymic atrophy appear to go hand in hand. Various forms of stimulation producing the one seemed always to produce the other, but the effect was, as they say, "mediated" through the anterior pituitary—here, as ever, the leader of the orchestra. Thus injection of pituitary A.C.T.H. was found to cause adrenal enlargement and at the same time thymic atrophy, together with general atrophy of the lymph nodes; but this lymphoid atrophy does not take place after removal of the adrenal glands. As would be expected, administration of cortisone causes thymic atrophy, whereas thymic hypertrophy and general lymphoid hyperplasia take place in adrenalectomized animals. Is it possible that here is a clue to a condition of lymphatism, or, in other words, adrenocortical deficiency, which has given rise to the clinical concept of status lymphaticus? Attention has been drawn to this by Dr. Ucko (1954).

Further research has been done on the relation of the thymus and other lymphoid tissue to the circulatory lymphocytes and the production of antibodies. Dougherty and White (1950) in particular have worked on the correlation of changes in the thymus and lymph nodes with alterations in the numbers of lymphocytes in the circulation. Working with rats and mice, these investigators have found that lymphoid involution is associated with lymphopenia and an increase in serum globulin, with the result that the antibodies in the gamma-globulin fraction concentrated in the lymphocytes were discharged into the blood. It follows, therefore, that after administration of A.C.T.H. or cortical extract there was enhancement of a specific defence mechanism of the body. It has even been claimed that after a single injection of adrenocortical extract into hyperimmunized rabbits high antibody titres were produced within six hours.

The pundits agree to the control exerted by the adrenal cortex over blood lymphocytes and lymphoid tissue, including the thymus gland, but they are not so sure about the release of gamma-globulin and the antibody production. It was not found to occur in the treatment of patients with A.C.T.H., although their lymphocyte and eosinophil counts were reduced.

It will have been noticed that, throughout this discussion, the thymus gland has been treated as if it were simply an aggregation of lymphocytes—as if it were just an enormous lymph node. But is it?

Embryology

At this point we must go back to the beginning and consider the embryology of the thymus, which obviously may have an important bearing on its ultimate function in the body. Many studies of the embryology have been made, but the most convincing account is that published by E. H. Norris in 1938. It is generally agreed that the thymus is derived from the third branchial complex—that is, from both the endodermal pouch and the ectodermal sinus in the embryo, in close association, therefore, with the other important epithelial organs, the thyroid and parathyroid glands. Norris found that the third cervical sinus is the primordium of the primitive thymic cortex, and the source of Hassall's corpuscles, which are so conspicuous a feature of the thymus under the microscope. The epithelium of the endodermal pouch gives rise to the syncytial cytoreticulum of the gland, the cells of which, though large, are much less conspicuous than Hassall's corpuscles in the normal gland, being overlaid by the masses of round cells or thymocytes, which form the bulk of the gland. These are of mesenchymal origin, and secondarily invade the gland after it has been entered by blood vessels and connective-tissue cells. Finally, the fibrous reticulum or framework is not derived from the epithelial elements, but from the connective-tissue cells in the adventitia of the blood vessels and in the capsule.

According to Norris no part of the thymus comes from the fourth cervical sinus of the embryo, though other observers (Gilmour, 1937) believe that a variable portion is derived from this source, this portion sometimes being situated in the neck in relation to the thyroid gland. The thymus always retains its close association with the thyroid and parathyroids. The upper ends of the two cornua or cervical parts of the gland are usually very close to the isthmus of the thyroid. The lower parathyroids very frequently travel down into the thorax with the thymus. Several times I have found parathyroid tissue in sections taken from the lower end of the thymus, that is, from the neighbourhood of the pericardium.

This complex structure may reasonably arouse the suspicion that the thymus may have a hidden function related to its epithelial elements, and that this may be exercised independently of the lymphoid portion, on which attention has been hitherto so exclusively focused. Let it be supposed that nothing was known of the function of the thyroid gland until it was noticed that hypertrophy of the gland was associated with the signs and symptoms of a heightened metabolism, which could be restored to normal by removal of much of the enlarged gland. It could then justifiably be deduced that the function of the thyroid was intimately connected with the normal metabolic processes. Again, let it be imagined that parathyroid function was entirely unknown until it was discovered that removal of a parathyroid tumour abolished all the signs and symptoms of excessive calcium excretion. It would then be reasonable to deduce that the normal parathyroid was concerned with the maintenance of a normal calcium level in the blood stream and of a normal calcium content in the skeleton.

Association with Myasthenia Gravis

It has long been known that the presence of a tumour of the thymus gland is sometimes associated with the signs and symptoms of the strange form of muscular weakness known as myasthenia gravis. Removal of a thymic tumour was then shown in 1936 by Blalock (1939), of Baltimore, to abolish the disease, and the same thing has been demonstrated again since then by a number of other surgeons. I have myself cured or alleviated the disease a number of times in removing over 40 thymic tumours from myasthenic patients. Is it then perhaps reasonable to deduce, with the thyroid and parathyroid analogies in our minds, that the normal thymus may through its epithelial elements exercise some control over muscle action at some stage of its history? This deduction is surely strengthened by the observation that the thymic tumour is, like the parathyroid tumour and the hypertrophied thyroid, composed largely or entirely of epithelial cells, derived apparently from the reticular cells formed by the embryonic endoderm of the third branchial complex.

In the thyroid usually, and in the parathyroid sometimes, the signs of overactivity occur without the formation of any actual tumour. In the same way myasthenia gravis has been completely or almost abolished in 65% of nearly 200 myasthenic patients from whom I have removed an apparently normal thymus gland—though other observers have called it "persistent" or have assumed that it was "enlarged." I have already tried to show you how difficult it is to arrive at a standard of normality in the size of the thymus, and that in fact it is much larger than it should be.

These facts associating the thymus with myasthenia gravis appear to me to be inescapable, though we are landed in a rather difficult region of physiological theory.

The current theory of the biochemistry of muscular action postulates the presence of a substance, derived from nerve tissue, known as acetylcholine, which by its action transmits the nerve impulse from the end-plate to the muscle fibre. Excess of acetylcholine is destroyed by its antagonist, an enzyme called cholinesterase, derived from the blood and connective tissues. Normal muscle action is maintained by the balance of these reactions, and an extraordinarily efficient mechanism it is in the healthy person. In myasthenia gravis the muscular weakness is remarkably variable in its distribution. Often it is restricted to the bulbar area—the levator of the upper eyelids and the extrinsic muscles of the eye being specially liable to be affected. In other patients the skeletal muscles may be profoundly influenced. Sometimes the laryngeal muscles are so weak that the patient cannot speak; in other patients these are quite unaffected. This variable incidence we cannot begin to explain on any current theory, but, in general, in myasthenia gravis there would presumably be either an excess of cholinesterase or a deficiency of acetylcholine, so that muscle action becomes impaired. It is believed that it is the acetylcholine which is deficient, since the condition is temporarily alleviated by the administration of neostigmine, which antagonizes the cholinesterase and so increases the action of acetylcholine. The deduction would therefore follow that the epithelial thymic tumour or the overactive thymus gland is producing a secretion which interferes with the production of acetylcholine; also that the normal thymus is exercising some sort of control over the neuromuscular mechanism, particularly perhaps in the foetus and infant, in which the gland is so conspicuous an organ. A considerable body of laboratory evidence is now accumulating to show that there is indeed some such abnormal product in the circulation of myasthenic patients. Professor Andrew Wilson *et al.* (1953) have even succeeded in preparing a potent extract from thymus glands which I have removed at operation. This extract they have found to depress contractions in muscle-nerve preparations to a degree comparable to that produced by tubocurarine, and they have even succeeded in paralysing frogs and small birds and mammals. They have found a similar potency in the thymus glands of apparently normal foetuses and infants. For larger supplies of the extract they have now turned to the thymus of the foetal whale.

There is clear evidence of a circulating hormone to be derived from observation of myasthenia gravis in pregnant women (Keynes, 1952). Usually if a myasthenic woman becomes pregnant she experiences an alleviation of her symptoms, as if the foetus were contributing something to the advantage of its mother or neutralizing something which she is producing in excess. Commonly, she relapses again a few days or weeks after the confinement. Conversely, there is also the undoubted fact that a myasthenic mother may give birth to a myasthenic infant, though the infant will completely recover and lose all symptoms in a few weeks, when it is no longer under the influence of the maternal circulating hormones.

The pathological and clinical (may I even say surgical?) approach has thus furnished us with a working hypothesis on which the function of the thymus gland may eventually be elucidated. There are still many difficulties in the way of a final solution, and progress is likely to be slow. It may be thought safer to return for the present to Galen's belief that the thymus is just a cushion to protect the great vessels from contact with the sternum. This would certainly save us all a great deal of trouble.

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THE STATISTICAL SIGNIFICANCE OF BIOLOGICAL DATA

BY

Sir ERNEST KENNAWAY, M.D., D.Sc., F.R.S.

(From the Department of Pathology, St. Bartholomew's Hospital, London)

During recent years increasing reliance has been placed by all biological research workers upon the estimation of statistical significance. This attitude, of course, is very desirable, but it seems to be leading to a deplorable tendency to regard all numerical differences which are not "statistically significant" as in some way unreal or inaccurate, or at any rate as suspect and unreliable, and hence of no value as a basis for any inferences. But such non-significant differences, if observed accurately, are facts, and are entitled to the consideration given to any other facts; they may be due to chance, but they may also reflect real differences, which may be quite large under some experimental conditions.

We are surrounded by immense numbers of small biological differences which exist, however difficult it may be to demonstrate them statistically. Some very interesting examples of minute differences have been collected from the literature by J. B. S. Haldane (1949). The increase in length of ceratopsian dinosaurs from 1.7 to 6.5 metres in 22 million years took place at a mean annual rate of 6.1×10^{-8} times the length, which was equivalent, at the beginning of the period, to an increase in length of 1 mm. in 10,000 years. A dimension (height of paracone—that is, mesobuccal cusp) of an upper molar tooth in the ancestors of the modern horse increased at a mean annual rate of 3.6×10^{-8}. Man himself has developed from his ancestors through changes of this type, and Haldane gives some estimates of the rate of this process. One is, of course, aware that a statistician is not likely to be consulted on the question of whether any change has occurred between two successive generations of an evolving vertebrate, but the illustration given above shows the fundamental importance of biological changes which, considered as isolated numerical differences, would be utterly "insignificant."

The effects of this aversion to observed small differences is most undesirable in cancer research, because it leads to the use of the strongest possible carcinogens in the largest possible doses in order to get a "result"—that is, something statistically significant which is therefore "something to publish" (Kennaway, 1948).

These very active carcinogens have now an adverse effect upon research. They have set a standard which is apt to induce neglect of less active compounds, although the latter type is that to which we are likely to be exposed ourselves. If a synthetic compound does not yield tumours in, say, 50% of animals in six months it may be supplanted by more active ones. The time has come to concentrate upon naturally occurring compounds, and tissue extracts, which produce tumours in, say, from 5 to 10% of the initial number of animals in two years. Thus the incubation period of 46 sarcomas produced in mice by subcutaneous injection of cholesterol in fatty media ranged from 11 to 29 months, with a mean period of about 19 months (Hieger, 1954). Hence the assessment of the carcinogenic power of such compounds depends upon the number of mice which live through the second year. Such work is wholly unsuitable for short-term grants. One would like to see a whole staff devoted for 10 years, with no obligation to publish anything during that time, to the search for carcinogens and co-carcinogens in human tissues.

The question, What quantities are "statistically significant?" is, of course, one for mathematicians alone; one may suspect that many persons use this term freely who have never given any very clear thought to its exact meaning.

I am indebted to Dr. Richard Doll, of the Statistical Research Unit, London School of Hygiene and Tropical Medicine, for valuable help in the preparation of this note.

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RESPIRATORY FAILURE IN THE ACUTE CASE OF POLIOMYELITIS*

BY

A. B. CHRISTIE, M.D., D.P.H., D.C.H.

Physician-Superintendent, Fazakerley Hospital, Liverpool

In the intellectual history of mankind there are happily periods when the energies of many minds run together and the filament of human thought lights up. These are the moments when an age shakes off the sensibilities of the past and proclaims a new outlook. If, in quality, the scientist cannot vie with the artist, he is not inferior in the intensity of his mental processes, and when the energies of many scientific minds are directed to one end the outcome may be comparable, at a different level, with a shift of thought in the artist's world.

To those of us who deal with poliomyelitis there can be little doubt that the advances of recent years are of basic importance. The virologist and the epidemiologist have each contributed, fortunately in a complementary manner. Tissue culture is obviously an immense aid to the virologist in his laboratory research, but it also enables him to promise increasing help to the epidemiologist in the field. The epidemiologist has traced the path of the virus and has worked out many of the probable details of infection: much is still uncertain, but the importance of close contact and the significance of the minor illness seem established. These points are, in turn, of direct importance to the virologist: tissue

*Read at a joint meeting of the Sections of Microbiology and Pathology and of Preventive Medicine and Infectious Diseases at the Annual Meeting of the British Medical Association, Glasgow, 1954.

culture may result in a safe and abundant vaccine, but without knowledge of epidemiological detail he could not use it with intelligence. And the same applies to the possible uses of gamma-globulin. It is fortunate, then, that both in the laboratory and in the field advances so full of promise have been made together.

In the laboratory and in the field—but at the bedside, what has been achieved? It is doubtful if, to date, a single case of poliomyelitis has been prevented. Nor can we feel assured that the incidence or the severity of the disease is decreasing: the contrary seems to be true. The attack rates per 100,000 population in the United States for the years 1949–53 were 28.3, 22.0, 18.5, 37.2, and 22.8 (Report, 1953). Denmark had its worst epidemic in 1952: the attack rate for paralysed cases alone was 58 per 100,000 for all Denmark, and for Copenhagen itself the figure was 106; of these paralysed cases, approximately one-third had respiratory embarrassment. The epidemic in 1953 was on a smaller scale, with an attack rate for paralysed cases of 13 per 100,000, yet in total numbers it had been surpassed only three times in Denmark (*Lancet*, 1954). In 1951, as in the rest of Europe, the non-paralysed cases greatly outnumbered the paralysed. In Liverpool the number of cases has always been, in comparison, quite trivial, but the figures indicating the relative severity of epidemics are of some interest. For the years 1948, 1950, 1951, and 1953 the percentages of cases with paralysis of those admitted to hospital were 71, 66, 33, and 72; the percentages with respiratory paralysis were 14, 7, 8, and 12.

There seems to be no definite pattern. Epidemiologists may disagree, but clinicians, I think, feel they have little to guide them with regard to either the size or the severity of the next epidemic. When it comes to treatment, we have seen not even the shadow of a specific remedy. The clinician must make his own preparation.

Factors in Respiratory Embarrassment

Death in poliomyelitis results almost entirely from respiratory embarrassment; in fact, in the diagnosis and management of the acute case there is no major difficulty or any fundamental difference of opinion until respiration is involved. When this occurs the clinician is faced with an acute clinical emergency in which there are many involved problems and only a few indefinite answers. Two primary principles are clear and may be stated at once: (1) when the muscles of respiration are weakened by paralysis they must be mechanically assisted; and (2) when the patient's airway is obstructed, it must be cleared. These two principles are simple, but their application to a patient may raise the most baffling problems. A consideration of the factors involved may at least help to illustrate the difficulties.

The free ventilation of the human body depends on (1) the ability of the respiratory muscles, mainly the diaphragm and intercostals, to carry out the essential thoracic movements; (2) an unobstructed airway; (3) the integrity of the respiratory centre; (4) the retention of the normal elasticity and plasticity of the lungs and thorax and the presence of a healthy respiratory epithelium across which gaseous interchange can take place; and (5) the unimpeded return of venous blood to the heart and the free flow of blood through the pulmonary bed.

In a case of poliomyelitis any or all of these factors may be involved, some as a direct result of the disease, some as a result of treatment, and some as a result of both. I propose first briefly to review each factor from the point of view of causation, and then to attempt to analyse some of the clinical states with which we have to deal.

Paralysis of Respiratory Muscles.—Involvement of the respiratory muscles results from direct damage by the virus. The clinical picture is relatively simple and the indications for treatment are clear—some form of mechanical assistance will probably be required. One must not be misled by *apparent* paralysis, when the real trouble is in the pharynx and the patient is afraid, consciously or unconsciously, to breathe.

Obstruction of Airway.—The airway may be obstructed by accumulation of mucus in the pharynx due to pharyngeal paralysis—a direct result of the disease. Here again the indications for treatment—postural drainage—are clear. Obstruction to the airway may result apart from pharyngeal paralysis: inability to cough as a result of respiratory muscle paralysis may lead to excess of secretions in the air passages, plugging of bronchi, and atelectasis. It is essential to sift out the factors concerned and to apply the appropriate treatment, as treatment of only one factor may add to the damage.

Involvement of Respiratory Centre.—The respiratory centre may be directly damaged by the virus; oedema of the brain due to circulatory changes may also play a part. The centre may also be subjected to gross biochemical abnormalities, especially in respect of oxygen and carbon dioxide concentration, and these may be due either to difficulties of ventilation as a result of paralysis or to mistakes in treatment.

Involvement of Respiratory Epithelium.—Anoxia due to any of the foregoing factors may lead to oedema of the pulmonary epithelium. This will impede gaseous exchange and also decrease the elasticity of the lungs, and both these will increase the anoxia. The use of a tank respirator against oedematous lung tissue or an obstructed airway will further increase the pulmonary oedema. Finally, it is possible that pulmonary oedema may be caused centrally by vagonuclear involvement by virus.

Reduction of Cardiac Output.—Artificial methods of ventilation affect not only the lungs but the other contents of the thorax. Both tank respirators and positive-pressure appliances may by pressure effects impede the return of venous blood to the heart and so add to anoxia from a fall in cardiac output as in shock. But shock may also result from involvement of cerebral centres by virus or from the gross biochemical abnormalities already mentioned. Diagnosis of shock is obviously not enough; it is essential to attempt to assess the primary cause. Astrup *et al.* (1954) admit that "there can be little doubt that manual positive-pressure ventilation . . . has given rise to many cases of shock."

The combined effects of the two foregoing factors may be seen in Table I.

TABLE I.—*Intrapulmonary Defects in Poliomyelitis*

Alterations in pulmonary epithelium	due to oedema—due to	Anoxia Changes in blood pressure due to shock Vago-nuclear involvement
Diminution of ventilating surface of lung	due to blocking of bronchi leading to atelectasis—due to	Increased secretions Inability to cough
Alterations in vascular flow	due to: Shock—due to	Anoxia CO_2 retention Virus invasion of brain
	due to: Poor cardiac return—due to	Effect of mechanical ventilation

Clinical Analysis

It can be seen that the background to the clinical picture may be very complex, and in practice the clinical analysis of a case is often extremely difficult: if a symptom is wrongly interpreted, disastrous errors in treatment may result. Anoxia, for example, although usually easy to diagnose in a patient, cannot be regarded as a clinical entity for which there is one clear remedy: it may result in several different ways in one patient, and several factors may be involved at once. Table II illustrates some of these factors.

Anoxia is often only one part of the clinical picture: carbon dioxide retention frequently accompanies it, and the relief of the anoxia alone will not lead to clinical improve-

TABLE II.—*Anoxia in Poliomyelitis: Causes*

- *Mechanical difficulties of ventilation* — due to:
  - Paralysis of respiratory muscles
  - Obstruction of airway:
    - *Pooling* in the pharynx from inability to swallow leading to aspiration of mucus
    - *Increased* bronchopulmonary secretion due to inability to cough, leading to plugging of bronchi and atelectasis
  - Unhealthy pulmonary epithelium, due to anoxia
  - Poor venous return to heart
- *Shock*— due to:
  - Anoxia
  - High CO_2 concentration in blood
  - Cerebral damage by virus
- *Therapeutic mistakes* — due to:
  - Unsuitable types of respirator, or wrongly applied, leading to underventilation

ment. The administration of oxygen to such patients may in fact produce coma: the anoxia is relieved by the oxygen and the patient becomes pink, but the anoxic stimulus to respiration is removed, with the result that respiratory excursions decrease and carbon dioxide retention increases. Whereas slight increases in the concentration of carbon dioxide act as a stimulus to the respiratory centre, very high concentrations have a narcotic effect leading to medullary depression, decrease in respiration, fall in blood pressure, and so to the anoxia of shock. Some of the factors involved may be seen in Table III.

TABLE III.—*Changes in Blood pH and in CO_2 Concentration in Poliomyelitis*

- *Acidosis*—due to:
  - CO_2 retention—due to:
    - Respiratory paralysis
    - Obstruction of airway
    - Underventilation
    - Administration of O_2 without relief of other factors
  - Lactic acid—due to: Anoxia of tissues
  - Retention of fixed acids—due to: Renal vasoconstriction of shock
- *Alkalosis*—due to: Low CO_2 tension—due to: Mechanical overventilation
- *High CO_2 concentration in blood* —leads to: Medullary depression and shock
- *Low CO_2 concentration in blood* —leads to: Cerebral vasoconstriction leading to cerebral anoxia

It will be seen that, in all the cases considered, difficulties may arise both from causes due to the disease itself and also from wrongly applied treatment. It is easy, for example, by using a tank respirator, to reproduce the movements of respiration, but it is extremely difficult to match the respiratory circulation or ventilation so produced to the pulmonary vascular circulation, which is beyond our control. Although the mechanical movement of the chest wall may appear to be adequate, underventilation or overventilation may in fact be present, adding greatly to the complexity of the clinical picture. It may be an advantage to consider briefly some of the ways in which this may come about.

The patient may be simply overventilated.—Loss of carbon dioxide is excessive, but oxygenation is adequate. This will develop when a tank respirator is used at too great pressure or speed.

The patient is overventilated but anoxic.—(*a*) Changes in the alveolar membrane reduce the transfer of oxygen but affect very little the excretion of carbon dioxide. (*b*) There is a deficiency of oxygen, relative to the patient's needs, in the inspired air. A patient with a high temperature and increased metabolism requires more oxygen than a patient with a normal temperature.

The patient is simply underventilated.—Carbon dioxide accumulates in the blood stream and there is some hypoxia.

The patient is underventilated but well oxygenated.—This can result when using a rich oxygen mixture: ventilation may be sufficient to maintain an adequate oxygen tension in the alveoli, but insufficient to remove enough carbon dioxide, which therefore accumulates in the blood stream.

These are far from being theoretical considerations. They are problems presented by every case undergoing treatment. If not thoroughly understood, they may readily lead to a completely false clinical assessment of a case, and to the continuance or exaggeration of therapeutic mistakes. Two examples will illustrate this tendency. (1) Drowsiness may be caused by CO_2 retention due to underventilation, but may also be caused by an encephalitic or thalamic element in the disease. (2) Restlessness may be due to anoxia, but may also be a symptom of overventilation. The necessity for correct diagnosis is literally of vital importance.

Team-work

In a superficial way the poliomyelitis patient with respiratory paralysis resembles patients suffering from other diseases. With his cyanosis and anoxia he may recall the chronic bronchitic bordering on cor pulmonale, and the administration of oxygen may be equally dangerous to both. With the grossly disordered chemistry of his blood stream he may resemble the patient with uraemia. In his disordered consciousness he may suggest a patient with brain abscess. But he differs from all three in that he is essentially a healthy patient with healthy organs, battling with an acute respiratory and circulatory crisis. His life depends on correct treatment. At the bedside, physician and anaesthetist aim at accurate clinical assessment, and not too far away they require assistance from many colleagues. To the physiologist and clinical pathologist they look for methods of measuring and interpreting the changes in their patient; at the bedside there is too much guesswork. To the virologist and pathologist they look for further understanding of the way the virus affects the brain; it is so difficult to distinguish pathological damage from physiological distress. The pharmacologist must advise on sedation and the use of drugs controlling blood pressure and temperature. With the microbiologist, he may yet find the secret within the cell itself; there respiration finally takes place and there virus competes with cell life. To understand the problems of respiratory poliomyelitis we need clinical co-operation and clinical imagination: *omni nunc arte magistra.*

Summary

The contributions of epidemiologist and virologist to the study of poliomyelitis have been complementary. The clinician, however, still has to rely on his own clinical resources.

The cause of death is respiratory embarrassment, and the clinical picture presented by a patient suffering from respiratory failure may be very complex. The factors necessary for the free ventilation of the body are efficient respiratory muscles, a clear airway, an intact respiratory centre, a healthy pulmonary epithelium, and a free flow of blood through heart and lungs. Any or all of these may be involved. Treatment directed to improve one factor only may cause clinical deterioration.

Anoxia must always be considered along with carbon dioxide tension, the *p*H of the blood, and shock. An understanding of respiratory physiology is essential to the safe use of any form of assisted respiration.

The problem of respiratory failure in poliomyelitis cannot be dealt with by clinicians alone. At the bedside, team-work between physician, anaesthetist, surgeon, and pathologist is essential.

In writing this account, I had a background of reading and discussion the sources of which I cannot now acknowledge. I have found the articles by Astrup *et al.* (1954) and by Steigman (1954) of immediate use. Some of the material was included in a report to the Liverpool Regional Hospital Board, under whose auspices I visited Copenhagen in 1953: it was written jointly with Dr. J. R. Esplen, consulting anaesthetist to the Fazakerley Group of Hospitals, and to him I am indebted for permission to use it, but far more for constant advice and collaboration in the management of our cases.

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TREATMENT OF SEVERE CASES OF RESPIRATORY PARALYSIS BY THE ENGSTRÖM UNIVERSAL RESPIRATOR

BY

CARL-GUNNAR ENGSTRÖM, M.D.

(From the Municipal Hospital for Infectious Diseases, Stockholm)

Respiratory paralysis is by no means exclusively a complication of certain infectious diseases—above all of poliomyelitis—but it represents in many medical and surgical ailments the decisive accident that causes the fatal issue. Apart from cardiac and circulatory failure, the arrest of spontaneous breathing is the most frequent cause of death. If it could be controlled, a way for later reconstitution of health would be opened for many patients. When respiratory paralysis is caused by lesions in the rhombencephalon it is not infrequently accompanied by other complications of a central origin, of which deglutitive insufficiency with its risk of aspiration, central circulatory failure, hyperthermia, and coma (or stupor) may be mentioned. Treatment then becomes an intricate and many-sided problem for both doctor and nurse.

During the years 1949 and 1950 Sweden was ravaged by severe, widespread epidemics of poliomyelitis, which offered a mass of material for study of these problems. At that time respiratory paralysis of poliomyelitis was treated at the Stockholm Hospital for Infectious Diseases with two types of cuirass respirators, called after their inventors Sahlin and Freiberger. In spite of supplementing this therapy with tracheotomy, the mortality from respiratory paralysis of central origin, with paralysis of deglutition and other symptoms of brain-stem encephalitis, was about 85%. Clinico-physiological studies on these respirator cases showed that the fatal issue was usually due to an increasing retention of carbon dioxide; application of an additional oxygen supply kept the oxygen saturation in the arterial blood at normal levels (Engström, 1950; Engström and Svanborg, 1950, 1952), as the following typical case history demonstrates.

A 35-year-old patient, pregnant for seven months, fell ill with poliomyelitis on November 6. Two days later a rapidly progressing respiratory paralysis with pareses of the upper extremities supervened. A body respirator was applied, artificial respiration being supplemented by oxygen through a nasal catheter. However, the patient could not synchronize with the respirator, she was restless, and obviously worse. On November 19 tracheotomy was performed because paralysis of the larynx was suspected. In spite of continual oxygen supply by tracheal cannula, blood transfusion, and intravenous drip infusion, her general condition continued to deteriorate. Death occurred at 6 p.m. the following day. At necropsy atelectases of the lungs, lung oedema, and cyanosis of organs were found.

As a result of these studies it was recognized that these body respirators were not sufficient for artificial respiration of severe cases, especially with regard to proper elimination of carbon dioxide. At this point I started trials with intermittent insufflation, and it soon became clear that the unfavourable influence of (purely inspiratory) positive-pressure breathing on the circulation could be avoided by completing the respiratory cycle with an active expiration (rhythmical compression of the thorax). Based on these experiences, a respirator was constructed (Engström, 1953) which produced an active insufflation and an active expiration either by compression of the thorax or by means of an intermittent negative-pressure phase.

Method

The respirator (Figs. 1 and 2) gives an active insufflation with a predetermined volume which is passed direct into the air passages by means of a face-mask, an intubation catheter, a tracheal tube, or an intratracheal cannula. The active expiration is produced by mechanical compression

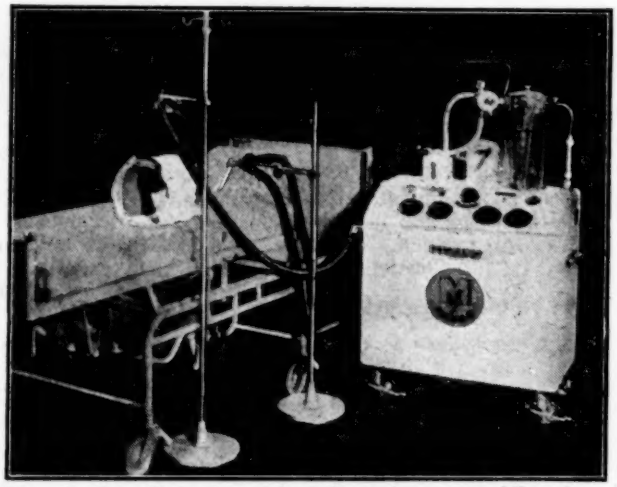

FIG. 1.—The Engström universal respirator providing intratracheal insufflation and active expiration by belt.

of the lower thorax by means of an inflatable belt or by use of a special accessory, the so-called Venturi suction apparatus (Engström, 1954) (Fig. 3). The latter applies intermittently an adjustable negative pressure direct into the air passages. For less severe cases the respirator can be used to drive a cuirass. The respiratory frequency, the volume insufflated, and the insufflation rate can be adjusted independently.

The direct insufflation method always permits the administration of a sufficient tidal volume. Since the insufflated volume can be exactly adjusted, adequate ventilation can usually be effected without the help of complicated laboratory control determinations. The rapid decline of the positive insufflation pressure, in combination with the active effect under the expiratory phase, impedes any dangerous rise of mean intrathoracic pressure, which is especially important in cases of impending circulatory shock (Maloney and Whittenberger, 1950). Oxygen can be added to the inspired gas in an exactly defined concentration.

In principle, insufflation is given by way of a half-closed system, thus avoiding the use of accessory apparatus for carbon dioxide absorption. The care of the patient is greatly facilitated by his easy accessibility, which among other advantages allows change of body position at will during treatment. The simple automatic control of resistance in the air passages greatly enhances effective supervision of the air passages in severe cases. The instrument was introduced at a session of the Swedish Medical Association on October 16, 1951 (Sjöberg *et al.*, 1952).

Clinical Experience

The first case treated with the instrument was that of a chronic respirator patient who, after more than 10 years' treatment with a cuirass respirator, contracted an acute complication in the form of a paralytic ileus, probably due to the passage of a renal calculus through the ureter.

The acute complication, which led to death within a few days, started with diarrhoea, pain in the epigastrium, and meteorism. Parallel with increasing meteorism, artificial respiration with the cuirass respirator became deficient, thus eliciting the signs of

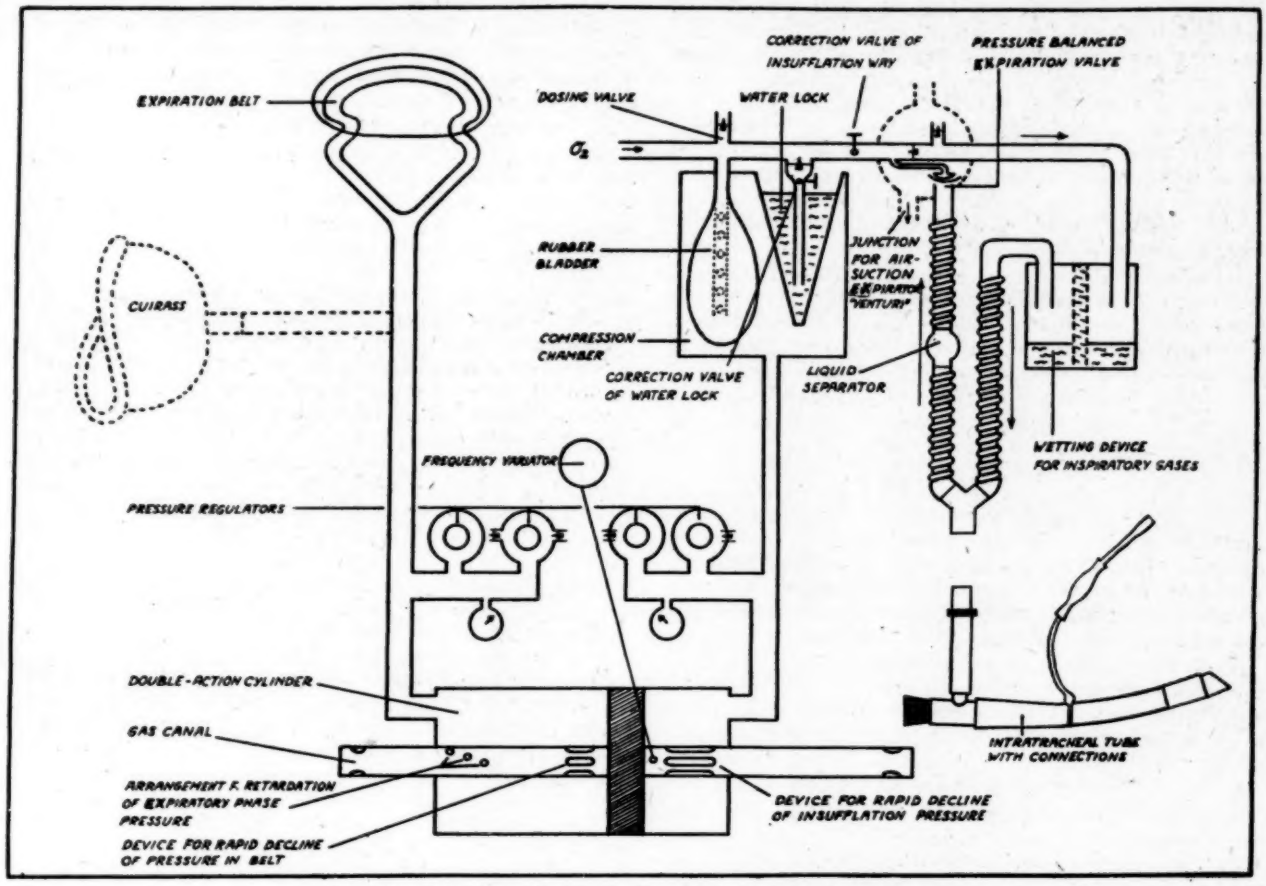

FIG. 2.—Principles of construction of the Engström respirator.

early asphyxia and impending circulatory collapse. Radiologically and clinically, a paralytic ileus was evident, the latter apparently becoming worse through the action of the respirator. Finally, treatment with the Engström respirator in combination with a face-mask and compression of the thorax by a belt was started on December 12, 1951. In this way the ventilation of the patient became immediately satisfactory, meteorism decreased, and his general condition improved so much that he was able to sleep during the following night for five to six hours, with the face-mask in place. After twenty-six hours' treatment his general condition was about the same as before the onset of the acute complication. However, he wished to have his old respirator again, after which the signs of ileus quickly increased. He died shortly thereafter in hypoventilatory shock.

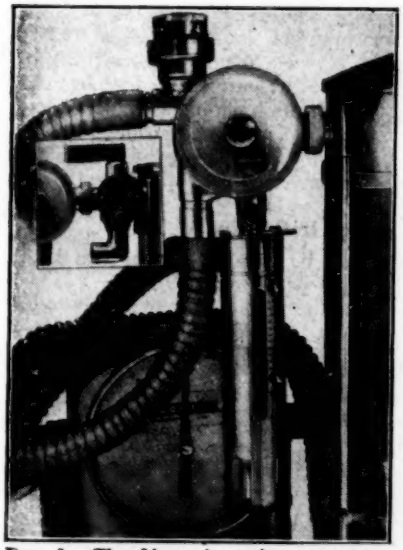

FIG. 3.—The Venturi suction apparatus for production of an active expiration by negative pressure in the airways.

Evidently the cuirass respirator had been unable to provide sufficient ventilation in this case; at the same time, because of its sucking effect on the abdomen, it potentiated the troublesome meteorism which impeded proper ventilation. A vicious circle was thus established.

During the severe poliomyelitis epidemic in Copenhagen in the autumn of 1952, the apparatus underwent further careful clinical trials at the Blegdam Hospital, where a great number of severe poliomyelitic respiratory paralyses were treated at that time. During this epidemic, as is now well known, a special form of intermittent manual positive-pressure breathing, derived from anaesthesiology, was adopted for the treatment of these cases after the usual tank respirators had proved wholly unsatisfactory (Lassen *et al.*, 1953). In this connexion a new technique for the control of the air passages was also developed, consisting of tracheotomy with insertion of a tracheal tube provided with an inflatable cuff. The Engström respirator proved to be the only completely automatic instrument appropriate for the treatment of the most severe cases (Astrup *et al.*, 1954).

1953 Poliomyelitis Epidemic in Sweden

During the severe poliomyelitis epidemic in Sweden in 1953 all 55 cases of bulbo-spinal respiratory paralysis (with one exception) admitted to the Hospital for Infectious Diseases in Stockholm between July 1 and November 15 were treated with tracheotomy and the Engström respirator. The mortality among these cases was 27% (Ström, 1953). All were cases in which respiratory paralysis was regularly accompanied by paralysis of deglutition, often also by central circulatory collapse, coma, encephalitis, or other symptoms of central nervous system involvement. In about 70% of the cases treatment had been started with a body respirator. Working with intratracheal insufflation and compression of the thoracic belt, the Engström respirator was able to produce, even during the most acute stage, an adequate ventilation without any sign of a noxious influence on the circulation. The reported mortality was mainly due to non-ventilatory complications such as hyperthermia, pulmonary infections, and occasionally to lung oedema.

Perhaps the deaths from hyperthermia could have been avoided by the use of the modern neuroplegic drugs which produce artificial hibernation, since the clinical course of this complication showed clearly that the rise of temperature was itself the deadly factor. The fatal cases of hyperthermia ran a course of continuous steady rise of temperature over three to four days with no recognizable sign of a causative infection in the lungs or elsewhere. Only when the temperature reached 41–42° C. did circulatory symptoms appear, leading rapidly, without the appearance of new signs, to death.

In the whole of Sweden the mortality for "bulbar cases" was 38% for the 1953 epidemic against 78% for the year before (Medicinalstyrelsen, 1954). A more careful analysis of the striking decrease in mortality has not yet been made. Treatment of the severe cases with the Engström respirator was largely introduced into the country in 1953.

At many places during this epidemic the treatment—at least in the beginning—was undertaken by personnel who had little experience with the problems of artificial respiration or with the technique for the control of air passages. In this connexion the stable ventilatory volume which the respirator provides and its simple means of control of resistance in the air passages proved very helpful. With the increasing experience of the doctors and nurses and their better understanding of the complications in the air passages and the lungs the mortality further decreased.

Apart from its use in the treatment of respiratory paralysis in poliomyelitis the Engström respirator has also been successfully used in the treatment of respiratory paralysis in polyradiculitis, barbiturate poisoning, skull traumas, etc.

Principles of Artificial Respiration

In assessing the value of artificial respiration from the physiological point of view consideration must be given to its effectiveness in regard to ventilation, quantitatively and qualitatively, and also to its effect on the circulation (Engström, 1953). The ventilatory action must be sufficient to ensure adequate elimination of the carbon dioxide formed in the metabolic processes, otherwise there will be increasing retention of carbon dioxide with consequent lowering of the blood *p*H and, finally, carbon dioxide narcosis; this phenomenon is often hidden by the simultaneous administration of oxygen preventing the development of cyanosis (Cara, 1954).

Carbon dioxide acidosis is now also a well-recognized clinical syndrome in certain cases of chronic hypoventilation in emphysema, pulmonary fibrosis, and bronchial asthma (Lovejoy *et al.*, 1954; Bühlmann, 1954). In more acute conditions, however, the importance of adequate carbon dioxide elimination is not yet always fully appreciated. Quantitatively the ventilation obtained should be such that the lungs are uniformly ventilated. If there is unequal distribution of the inspired gas, with hypoventilated and hyperventilated regions in the lungs, there will be partial shunting of the blood in the pulmonary circulation. In the presence of a shunt of this kind, and with atmospheric air as the breathed gas, deficient oxygenation of the blood passing underventilated parts of the lungs will not be compensated for by hyperventilation of other parts. There will consequently be a diminution in the oxygen saturation of the arterial blood. As regards the elimination of carbon dioxide on the other hand, the deficient elimination due to hypoventilated parts of the lungs may to a large extent be compensated by increased carbon dioxide elimination in hyperventilated parts. Anoxaemia may in such cases often be overcome by an extra supply of oxygen, but there is then a great risk of atelectasis.

Even in spontaneous respiration pressure and flow in the respiratory and circulatory systems are intimately related with each other; under normal conditions, however, the influence of respiration on circulation is slight and is readily compensated by adaptive mechanisms (Lauson, 1946). The circulatory action usually encountered in the different forms of artificial respiration consists in influencing the cardiac output as a result of changes in the intrathoracic pressure caused by the respirator. A lowering of the cardiac output in intermittent positive-pressure breathing is due to impeded return of the venous blood to the heart and is directly related to the magnitude and duration of the pressures applied (Werkö, 1947). High pressures and a long inspiration phase may greatly diminish the cardiac output, which can lead to circulatory shock; prolonged treatment with this form of artificial respiration, especially if there is in addition some sort of expiratory resistance, makes this injurious effect on the circulation particularly apparent (Maloney *et al.*, 1951).

In intermittent positive-pressure breathing accompanied by passive expiration the breathing level is displaced in the inspiratory direction. Proportionately greater pressures will thus be required to produce the same changes in volume, a condition which is shown by the pressure-volume curves of the ventilation of the lungs. An active expiratory phase lowers the breathing level and, proportionately, the magnitude of the positive pressure required to produce the same ventilatory effect (Maloney *et al.*, 1953). Investigation of the intratracheal and intraoesophageal pressures—the latter as a representative of intrathoracic pressure conditions (Ferris *et al.*, 1952)—has shown that intrathoracic pressure can in fact be lowered by the application of an active expiration, for instance, by means of suction during expiration (Fig. 4). The effect on the circulation parallels the changes in mean intrathoracic pressure; elevation of this value impedes venous return to the right side of the heart and diminishes cardiac output; as a compensative mechanism the peripheral venous pressure is increased. However, this mechanism depends on the integrity of circulatory control. In shock and in the presence of considerable blood loss it is often deficient.

If a respirator is to have universal application in treating even severe respiratory paralysis, it must satisfy the following requirements: (1) exercise great ventilatory action; (2) produce uniform pulmonary ventilation; (3) act in such a way that no difficulty of synchronization occurs with the patient's spontaneous breathing; (4) produce adequate ventilation without harmful effects on the circulation; (5) its method of operation should not be harmful to the elasticity of the lung tissue; (6) its application should be independent of the patient's posture; and (7) it should produce a high degree of relative humidity in the respiratory gas administered directly into the air passages.

Types of Respirator

In general, respirators can be classified under two main groups. (1) Body respirators with which ventilation is obtained by changes in pressure over the entire body surface or

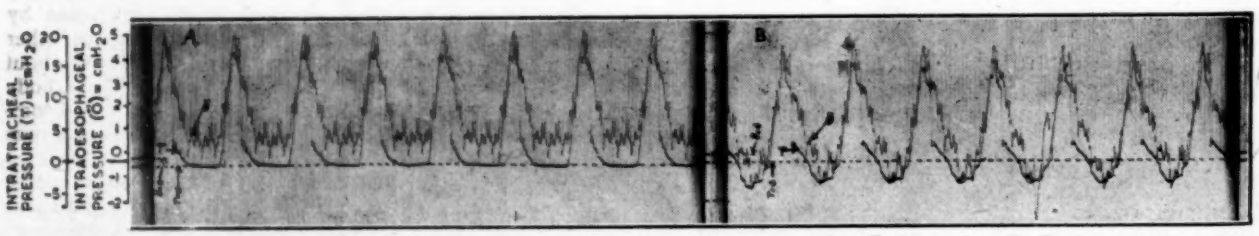

FIG. 4.—A. The intratracheal and intraoesophageal pressures with positive-pressure insufflation only. B. Same pressure curves with application of an active expiration by means of the Venturi suction apparatus. Note conspicuous lowering of level in both curves.

parts of it; their range goes from "sealed rooms" through the "iron lung" to the chest or abdominal shells and the chest–abdomen cuirass. Body respirators have mainly inspiratory action; in some types inspiration can be supplemented or replaced for a short time by a positive-pressure attachment. (2) This group is represented by insufflation respirators, which may be either positive-pressure apparatus, giving only active inspiration, or combined positive/negative-pressure machines, giving an active expiration as well. As the body respirators have almost unanimously been abandoned for the treatment of acute and severe cases of respiratory paralysis, this discussion is limited to explaining the essential differences between the two types of clinically introduced and commercially available insufflation respirators.

In pressure-cycling apparatus (Mushin and Rendell-Baker, 1954) the ventilatory effect depends not only on pressure variation but also on airway resistance and lung compliance. Increased resistance in the tracheo-bronchial tree means diminished efficiency of ventilation; theoretically ventilation could be made efficient if these factors could be held constant. This is, however, impossible in acute conditions. Leakage in the positive pressure phase prolongs inspiration time; with a big enough leak the valve does not operate, resulting in a constant pressure application (with subcycling values); this might rapidly become very dangerous in the presence of certain complications and circulatory lability. Concerning the circulatory effect of such systems, it has been emphasized (Maloney *et al.*, 1953) that it is important to add a negative phase in order to keep the mean intrathoracic pressure at low levels, which will avoid the harmful effect of positive pressure on the circulation.

The Engström respirator, on the other hand, delivers a predetermined volume at a pre-set frequency. That means that the machine furnishes the pressure needed to overcome the resistance, the latter being recorded on a water manometer so that any developing impediment can be observed. Therefore, the apparatus represents a time and volume cycling respirator, and is the first of this type used clinically and on a large scale. It ensures a quantitatively sufficient ventilation to the patient with a predetermined volume of any desired qualitative composition.

Conclusion

The severe forms of respiratory paralysis in which signs of central lesions are prominent often constitute a rather complicated therapeutic problem for both physician and nurse. The reported method of treatment has been widely adopted in the Scandinavian countries during the past years, and has led to a considerable decrease in mortality. It must be pointed out, however, that artificial respiration is but one side of the intricate therapeutic problem in these cases; the rest of the treatment is at least as important, particularly the control of parenteral nutrition, water and mineral balance, and the maintenance of an adequate air-way.

Summary

The Engström respirator is described, and the results obtained with it at the Stockholm Hospital for Infectious Diseases in a series of 54 consecutive cases (mortality 27%) of acute, severe poliomyelitis with brain-stem involvement are reported. The respirator is suitable for the treatment of all forms of severe respiratory paralysis, such as may occur in polyradiculitis or barbiturate poisoning, for example.

The principles on which satisfactory artificial respiration depend are discussed.

Finally, it is stressed that, in addition to respirator therapy, efficient general medical treatment is essential to success.

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THE PREVENTION OF DEFORMITY IN POLIOMYELITIS*

BY

J. M. P. CLARK, M.B., F.R.C.S.

Assistant Orthopaedic Surgeon, Leeds General Infirmary

It is axiomatic to state that it is better to prevent deformity rather than try to correct it after it has occurred. But the idea is commonly honoured only in the breach. It is too often convenient both for the conservative surgeon and for the timid patient to be lulled into a state of hopeful security by the thought that physiotherapy will not only restore strength but will also prevent deformity. Early surgery is often regarded as interference, and it is usual to recommend that anything more drastic than manipulation ought to be relegated to the stage when muscle recovery is complete. Theoretically this interval may extend to two years, but as a practical policy it is fair to consider all worth-while muscle recovery to be achieved by the end of six months from the onset of the disease. Since the orthopaedic requirements for nursing during the acute phase of the disease have become more generally recognized, surgical adjustment of potential deformity depending upon muscle imbalance can usually be safely left until six months have elapsed, by which time a clear assessment of muscle recovery will have been made. But there are other perhaps less potent, but not negligible, causes of deformity that will require attention before the effects of muscle imbalance are likely to become clearly manifest. In any event it seems only logical to treat and to attempt to counteract any condition or force that will otherwise inevitably produce deformity in the fullness of time. The need for early recognition of real or potential deforming influences is the strongest argument that can be offered for the inclusion of the orthopaedic surgeon in the team of experts that the management of poliomyelitis calls for from the very beginning.

Causes of Deformity in the Acute Phase

Pain.—It is too often forgotten that in a relatively small proportion of patients poliomyelitis is a painful disease, and that in a few of these the pain may persist after the febrile attack has subsided, even up to six or eight weeks after the onset of the disease. Pain means immobility on the part of the patient in whatever position may be found to be comfortable. Pain also means that any attempt to carry out passive movements in order to dispel peri-articular

*Read in the Section of Orthopaedics at the Annual Meeting of the British Medical Association, Glasgow, 1954.

oedema and to limit joint stiffness is likely to be resented. With persuasion the important passive movements can and must be carried out and their range gradually increased. Complete immobility caused by pain requires splintage for the joints and limbs in their positions of optimum function until the pain can be relieved enough by local heat and sedatives to enable passive movements to be started.

Muscle Spasm.—This has been a subject for controversy probably because it is so easily confused with tightness. In 1947 Seddon found that muscle shortening occurred in 10 out of 1,500 patients, and in none was spasm unequivocal. In any event muscle spasm subsides very quickly and if protracted it is probably by psychogenic perpetuation. In the unit at Pinderfields I have seen the condition only once in over 900 patients. One leg was affected for almost six months, and in consequence the knee was held in full extension and the ankle in full plantar flexion. The spasm finally resolved after repeated paravertebral blocks, using local analgesic, and eventually there were no residual deformities in the affected limb. Temporary spasm recurred once after accidental sudden stimulation of the leg with a stream of cold water, which suggests that there remained a preternatural irritability of the muscles.

Fibro-Elastic Tissue Contractures.—The tightness produced by these contractures is so usual that poliomyelitis ought to be regarded as a disease of the collagenous tissues as well as of the motor nervous system (Bennett, 1952). The changes in the fibro-elastic tissues are early and rapid and result in early shortening and loss of normal elasticity and resilience in tendinous, ligamentous, and fascial structures; they occur far too soon to be manifestations of disuse and postural adaptation.

Sites of Potential Deformity from Collagenous Contracture

The sites most affected are the plantar fascia, the tendo Achillis, the ilio-tibial band, the hamstrings, the lumbosacral fascia, and the peri-articular ligaments of the spine. The less affected sites are the infrapatellar tendons, the pectoral muscles, teres major, and pronator teres.

If the sites likely to be affected are examined as a routine early contractures will not infrequently be found. It is probable that contracture of the peri-articular structures of the spine is a prime cause of spinal deformity. At any rate when scoliosis does occur and is developing it is the result of a nice mixture of peri-articular contracture and imbalance of the intrinsic muscles of the spine. A similar mixture of contracture and paralysis has to be taken into account with regard to the forces responsible for maintaining a normal relationship of the pelvis to the spine.

The recognition of these early contractures goes far to prevent the development of deformity on their account. Passive, and, later, active stretchings of the tightening structures can be expected to be effective only in the early stages. Established deformity will require tenotomies and fasciotomies, which generally speaking ought to be avoidable. It must be recalled, however, that the modern treatment of respiratory paralysis from poliomyelitis has introduced a new engine for producing deformities in the shape of the cabinet respirator. Consideration of the effect and site of collagenous tissue involvement makes it clear that it will be impossible to avoid the development of certain deformities in patients who need to be isolated in the cabinet respirator for any length of time. Such deformities are avoidable and treatable only by redesigning the respirators with this in view, and the problem is receiving attention.

Passive stretching of early or potential fibro-elastic contractures is the preventive treatment of choice, but it is a two-edged weapon. In the hands of ignorant or irresponsible therapists stretching will result in muscle tears which will not only destroy valuable muscle fibres required for future rehabilitation but will also produce scar tissue and thus eventually exacerbate the condition it was intended to ameliorate. Particular care must be exercised in stretching until the return of power of the controlling muscles is fully known, and only sufficient range of movement ought to be obtained at first to enable muscle action to begin. In the established contracture passive stretching can only do harm to the muscles and will have no effect at all on ligamentous bands or aponeuroses.

The acute phase of the disease is completed at the end of an arbitrary period of three weeks or a month after the onset of the disease. The next phase of potential recovery is heralded by an estimation of the muscle power, and its distribution and the presence of any deformities are noted. This is the period when, if possible, definitive correction of existing deformative factors should be carried out and the slow formation of new deformities prevented.

The causes of deformity in the phase of potential recovery are: uncorrected fibro-elastic tissue contractures, muscle imbalance, and perverted action of normal muscles and tendons.

Contracted Bands

The chain of deformities that a contracted band can produce must be recognized so that any particular deformity can be related to the single prime cause. Similarly the chain of deformities that can result from overstretching the controlling muscles must be known in order to avoid the evil results of maltreatment. This principle is most convincingly seen with regard to the tendo Achillis and its controlling triceps surae (see Table I), and with the ilio-tibial band and its two motors, tensor fasciae femoris and gluteus maximus.

TABLE I.—*Tendo Achillis*

Contracture	Overstretching
varus	varus
Equinus	Calcaneus
valgus	valgus
Genu recurvatum	Cavus

After detecting apparent contracture of the tendo Achillis it is next essential to obtain a clear idea of the power of the gastrocnemius and soleus, which together constitute the triceps surae and work as a unit in pulling on the calcaneum. The power of the posterior tibial muscles must be equally accurately measured and their power relative to that of the triceps surae assessed. The importance of this lies in a disparity of power in favour of the posterior tibial musculature because that will increase any calcaneus deformity permitted by a weak triceps surae or an overlong tendo Achillis (Fig. 1). The posterior tibial muscles in attempting to supplement the weak triceps surae will actually exacerbate the deformity.

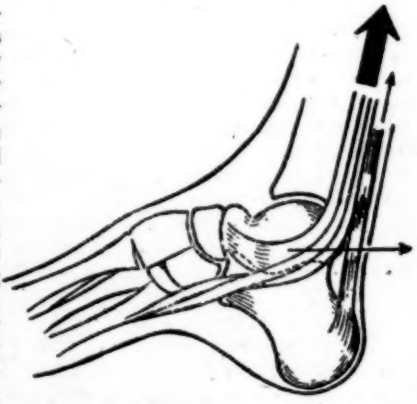


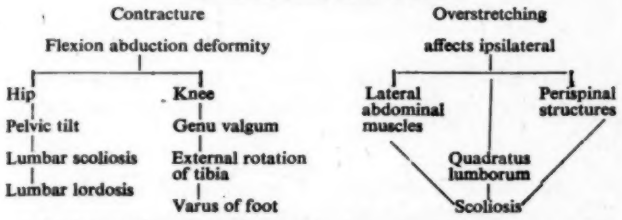
FIG. 1.—Lateral view of ankle in calcaneus to show the action of strong posterior tibials to increase the deformity.

I have on more than one occasion found physiotherapists industriously manipulating feet into dorsiflexion with the object of stretching the plantar fascia. Unless the hindfoot be firmly grasped there will be gradual lengthening of a weak triceps surae and consequently a troublesome calcaneus deformity.

The ilio-tibial band, by reason of its attachment through its motor muscles to the pelvis and by its insertion to the head of the tibia, acts upon both hip and knee. Even when the buttocks and thighs are severely paralysed the tensor fasciae femoris is commonly spared because of its long cell station in the spinal cord. In consequence a combination of

fibroelastic tissue contracture and the preservation of one motor muscle in opposition to much reduced power will produce a chain of deformities (see Table II).

TABLE II.—*Ilio-tibial Band*



Flexion deformity of the hip is more commonly caused by contracture of the ilio-tibial band than by shortening of the hip flexors or periarticular structures. This is demonstrable by the ease with which the flexion deformity can be abolished by widely abducting the hip. It is rare to require section of the ilio-psoas muscle (which is the only real hip flexor) to correct a flexion deformity of the hip, and the sartorius plays no part at all in hip-flexion deformities. Soutter's (1914) operation (or its modifications) is to be condemned for muscle destruction because the contractures lie in the fascia and intermuscular septa and the muscle fibres are normal. Ilio-tibial band contractures cannot be corrected by passive stretchings but only prevented; nor can they be overcome by the application of serial plaster spicas. The established contracture of the ilio-tibial band is best treated by using Yount's (1926) operation. The ilio-tibial band is divided in its lower part, 4 in. (10 cm.) above the knee-joint, the lateral intermuscular septum is excised down to the femur, and the fascia covering the vastus lateralis is sectioned in front and behind.

In total or subtotal paraplegia much thought must be given before breaking down a tight fascial envelope of the thighs and buttocks. In the absence of effective muscle power such an envelope is useful in the prevention of "jack-knifing" when the patient is trying to use callipers; intact contractures may obviate the need for a pelvic band and hip-lock attachment to the callipers. It is often a nice decision whether to have ease in sitting at the expense of an inability to perform four-point, or even three-point, walking.

Muscle Imbalance

When it has become clear from a consideration of the muscle chart that there is obvious muscle imbalance in a part then deformity can and must be anticipated. Muscle rehabilitation in the presence of imbalance can only make matters worse by strengthening the pull of the stronger muscles at the expense of the weaker. Early tendon transpositions are frequently called for, especially in children, in order to preserve satisfactory function, but it is better to avoid operation under the age of 5 years if possible because of the difficulty of muscle re-education in the very young.

Operations to improve the muscle control of the shoulder are not indicated, except transposition of the teres major to the lateral aspect of the humerus to prevent internal rotation deformity of the arm. Early restoration of active flexion in the elbow, preferably by pectoral muscle transposition, is desirable where possible because a working biceps will also give active supination. In default of this, transposition of the flexor carpi ulnaris to the dorsum of the lower end of the radius is effective in correcting a pronation deformity. For the control of the wrist an equable distribution of available muscles must be arranged to give flexion and extension without deviation. Wrist flexors can be transferred into finger extensors because they normally act synergically; to a lesser degree wrist extensors are suitable for depleted finger flexors; the pronator teres works well as a wrist extensor. Care must be exercised to avoid the subtraction of all wrist flexor power, otherwise a hyperextension deformity of the wrist will ensue associated with complete extension of the fingers at the metacarpo-phalangeal joints. Loss of opposition is the commonest residual paralysis of the hand in poliomyelitis; it reduces the power of pinch by 90% and leaves an apposition deformity. Every effort must be made to restore active opposition by transposing a motor tendon to work from the region of the pisiform bone and, by its attachment to the ulnar border of the base of the proximal phalanx, to restore the rotation of the thumb on its own axis.

In the absence of pelvic obliquity caused by contractures of the ilio-tibial band most scoliosis is caused by defects in the spinal structures. When it is known that there is imbalance of the paravertebral muscles or the intrinsic muscles of the spine treatment is not very effective unless the degree of imbalance is small. The most effective measure is to nurse the patient in a hammock in the overcorrected position.

It is also necessary to maintain a balanced active relationship between the pelvis and thorax. Unequal paralysis of the lateral abdominal muscles is best corrected by transposition of the ilio-tibial band (keeping the tensor fasciae femoris and its nerve supply intact) to the ninth rib in the mid-axillary line. Forward tilting of the pelvis in the presence of equal weakness of the lateral abdominals will benefit from bilateral operation, and the improvement in balance and thoraco-pelvic stability will do much to help the gait.

Leg deformities are not usually caused by muscle imbalance, but where there is gross preponderance of the hamstrings the transposition of the biceps and semitendinosus to the patella is a good method of supplementing a weak quadriceps; the semimembranosus must be preserved intact in order to avoid the development of genu recurvatum.

Tendon transposition in the foot has much to offer either as a supplement to the action of synergistic muscles or to an arthrodesis of the foot (Table III). There is no tendency for transposed tendons to lose power when they are acting naturally, but when the new location requires education of

TABLE III.—*Tendon Transpositions in the Foot*

Group	New Insertion	Deformities Controlled
Anterior ..	Dorsum of foot	Equinus, valgus and varus
Posterior ..	Tendo Achillis	Calcaneus
Toe extensor ..	Calcaneum Dorsum of forefoot	Claw toes

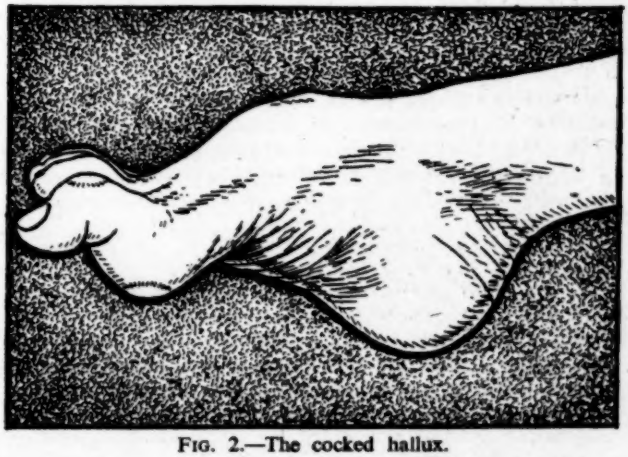


FIG. 2.—The cocked hallux.

the muscle to act with an antagonistic group a material loss of power is to be expected. It is not enough to allow a foot deformity to develop with the idea that it can be corrected and fixed by arthodesis later because muscle imbalance can still act as a deforming agent when the joints are fused. Muscles must be so balanced that the maximum of power of active dorsiflexion and plantarflexion can be achieved and yet the foot be maintained plantigrade.

The results can be improved by making use of synergy of neighbouring tendons. Transposition of the extensor hallucis longus and peroneus longus or transposition of both peroneals medial to the midline of the foot are examples for replacement of weak or paralysed tibialis anterior.

Analysis of the deformations is most important. For instance, the dropping of metatarsal heads may be secondary to cavus induced by an uncorrected calcaneus deformity. Dropping of the first metatarsal head is a very common deformity which will inevitably produce a cocked hallux (Fig. 2) with its painful friction areas, plantar callus, and ruinous wear on the shoe sole.

Perverted Action of Normal Tendon

Two prime examples of this are to be seen in the foot. One has already been noted in the discussion of the calcaneus deformity. The posterior tibial muscles, in the presence of a weak triceps surae, will attempt to take over the function of the weak group. If the calcaneum is already dorsiflexed then the action of the posterior tibial muscles will exacerbate the deformity and the need to transfer the posterior tibial muscles to the tendo Achillis is paramount.

FIG. 3.—Gross valgus foot with perverted action of extensor digitorum longus tendons and peroneus tertius.

The other example in the foot is the action of the extensor digitorum longus tendons and peroneus tertius on a valgus foot resulting from a weak tibialis posterior (Fig. 3). If this action is allowed to persist the foot will assume a bow shape and the long toe extensor tendons will act as the bow string. Mistakenly the peroneal tendons may be used to counteract the deformity, but it will persist if the true deforming agent be not perceived. The foot can only be corrected by shifting the toe extensor tendons to the medial side of the foot to act as a supplement to the weak tibialis posterior.

Summary and Conclusions

The causes of deformity during each phase of poliomyelitis are considered. In the acute stage the effects of pain and muscle spasm are discussed, the contracture of fibro-elastic tissues is detailed, and methods of its control are outlined. In the stage of potential recovery the mechanics of uncorrected fibro-elastic contractures are elaborated and methods of correction are recommended. Muscle imbalance as a cause of deformity is expounded and the surgical correction by tendon transposition is explained as a means of anticipating common deformities. The perverted action of normal tendons caused by paralysis or weakness of other muscles is instanced and its correction is described. The thesis is that surgical anticipation of deformity is more logical and easier to perform than surgical reconstruction, and the results are better.

It is not claimed that all deformities can be controlled by preventive surgery, but it is maintained that patients can be halted in a steady deterioration which would otherwise yield an intractable problem. In poliomyelitis it is the surgeon's duty to anticipate rather than to reconstruct.

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POSITIVE-PRESSURE INFLATION IN RESPIRATORY PARALYSIS OF POLIOMYELITIS

BY

LUISE WISLICKI, M.D., D.A., D.T.M.&H.
Anaesthetist, Rothschild Hadassah University Hospital, Jerusalem, Israel

During the 1952 epidemic of poliomyelitis in Denmark the iron lung type of respirator used in cases of bulbar respiratory paralysis requiring tracheotomy was replaced by a different method of artificial respiration. Instead of the application of negative pressure to the chest wall manual rhythmic positive-pressure inflation of the lungs themselves was performed. It was carried out, by means of an apparatus specially designed by Dr. B. Ibsen (Lassen, 1953), through a cuffed endotracheal tube led into the tracheotomy opening.

Since that time various other methods of artificial ventilation in these cases have been described. Macintosh (1953) redesigned the bellows part of the Oxford vaporizer as a separate unit which he called the Oxford inflating bellows and which are operated by hand. Mushin (1953) added to these the Cardiff inflating valve which automatically allows deflation and prevents rebreathing. Russell and Schuster (1953) constructed a respiration pump which drives the Oxford bellows automatically. Others constructed automatic respirators for inflation where volume, speed, and pressure were either set according to the needs of each case or steered by the intrapulmonary pressure of the patient (Pask, 1953; Beaver, 1953; Bang, 1953; Macrae *et al.*, 1953).

I have utilized the original Oxford vaporizer fitted with a Salt valve (Wislicki, 1953). Its use for two different purposes is described in this paper.

Case 1

A builder aged 29 was admitted to the local infectious diseases hospital on October 29, 1953. For four days he had suffered from poliomyelitis which had resulted in paralysis of both legs and retention of urine. His temperature was 102.6° F. (39.2° C.). During the next two days external eye muscles and pharyngeal muscles became affected, causing diplopia and difficulties in swallowing, respectively. Large amounts of mucus accumulating in his mouth and pharynx necessitated tracheotomy (Dr. A. Fraenkel). On November 1 partial respiratory paralysis of bulbar origin developed. Manual artificial respiration was applied, but his condition deteriorated and little hope was held out for his survival. I was then called in.

On arrival I found a patient of muscular build, in a good state of nutrition, but cyanosed, restless, and with a very anxious expression. His respirations through a tracheotomy opening were laboured, irregular, and shallow. It was decided to try artificial respiration by means of the Oxford vaporizer. As no cuffed endotracheal tube was available the inner tracheotomy cannula was removed while the outer one was left in position. A Magill endotracheal tube No. 5, shortened to 10 cm., was inserted into the cannula until it made a tight fit. The tube was connected by a Rowbotham connexion and a short piece of wider rubber tubing to the Salt valve and from there to the Oxford vaporizer. Rhythmic inflation with air only was started. After a few minutes oxygen at the rate of about 2 litres a minute was led into the vaporizer. Suction was performed by taking the rubber tube out of the tracheotomy cannula and introducing the suction catheter instead. The mouth and pharynx were also cleansed by suction when secretions accumulated.

Within ten minutes improvement in the patient's condition was striking. Cyanosis and restlessness had decreased considerably, and he indicated that he felt much easier. Inflation and suction were continued for one hour, and then auxiliaries were trained to continue artificial respiration at the rate of 20 a minute. An hour later the patient was asleep and of excellent colour.

He was kept on constant manual inflation of the lungs for forty-eight hours. His bulbar paralysis receded gradually and he could then be left on spontaneous respiration for ten minutes out of every hour. At the beginning of each period his respirations were deep and satisfactory, but they weakened gradually, and he asked then for renewed inflation. After a further twelve hours he could be left on spontaneous respiration for two hours, and about eighty hours after artificial ventilation had been started no further help was required. His temperature fell gradually to 99° F. (37.2° C.) and the power of swallowing returned. On November 6 the tracheotomy cannula was removed. He continued with subfebrile temperatures for a few days. There was no recurrence of respiratory embarrassment. At the beginning of December he was generally very well, with normal vision, and had regained control of his bladder. Unfortunately, his legs were still paralysed, with only slight movements in the right leg.

Case 2

A man aged 25 had been in the iron lung for several days suffering from poliomyelitis with paralysis of all limbs, intercostals, and diaphragm. Swallowing was impossible, and almost constant oral suction had to be applied because of continuous outpourings of large amounts of mucus. Tracheotomy had not been performed. On November 2 I was asked to pass an endotracheal tube in order to suck out his trachea and bronchi. Respiration in the iron lung had become unsatisfactory, he was in great distress, and it was thought that mucus had entered his respiratory passages. Oral intubation under local analgesia with 5% cocaine was performed. Though the air passages were found to be almost clear, intubation resulted in immediate relief. Ventilation had become inefficient because the entrance to the larynx had been partly closed by the tongue, which had fallen back owing to partial paralysis of the muscles inserted at the hyoid bone. The endotracheal tube pushed the tongue forward and provided an open airway. The patient's condition improved, he slept for five hours, but then the tube started to disturb him and had to be removed. Obstruction of the airway did not recur.

Two days later several attempts were made to introduce a stomach tube with the help of a laryngoscope in order to feed him. They failed because, owing to paralysis of the pharyngeal constrictors, the tube was not guided down the oesophagus but rolled itself up in the pharynx. It was then decided to make a feeding gastrostomy. He was again intubated under cocaine analgesia, and the tube was connected to the Oxford vaporizer. At first, respiration through the vaporizer was synchronized with that of the iron lung, as it was thought advisable to continue in the rhythm to which the patient had been used. The motor of the iron lung was then switched off and the effect of inflation with air was tried. It became clear at once that this was not enough. The patient's colour deteriorated and he showed air hunger. As no cuffed endotracheal tube was available to close the trachea, too much air returned along the wall of the ordinary tube without reaching the lungs, and the part which reached the alveoli did not provide enough oxygenation. A pharyngeal pack was ineffective because it became soaked through with mucus after a few moments. Oxygen was led into the vaporizer in increasing quantities, and at a very high rate of flow the patient could be kept in a fairly satisfactory condition.

Gastrostomy was performed (Dr. W. Nissel) under local analgesia. It was carried out in three stages, as the iron lung had to be closed twice during the operation in order to give the patient a more thorough ventilation. By this manœuvre it was possible to complete the gastrostomy. He recovered quickly from the operation and has been fed through the opening now for four weeks. At the time of writing his general condition was still very poor.

Discussion

Both of these cases are instructive. In Case 1 manual inflation was carried out with very crude means, as a sudden and unprepared start had to be made. It showed that a cuffed tube is not essential for inflation through a tracheotomy opening. The shortened endotracheal tube pressed into the outer cannula fitted tight enough to carry out artificial inflation over a protracted period. The cannula itself blocked the trachea effectively against secretions from above. As no suction on the thorax was applied, and air under positive pressure entered only below the larynx, secretions from the mouth and pharynx were not forced past the cannula, while oral and pharyngeal suction sufficed to prevent a trickle down the trachea. The system adopted out of necessity actually proved an advantage. A cuffed tube would have been unknown to the available personnel and most likely some accident would have happened. But they were used to performing suction through a tracheotomy cannula and no difficulty was experienced.

It took about half an hour to train auxiliaries. They were only shown how to press the bellows and close the valve simultaneously at a given rate. Once the technique was understood inflation proceeded smoothly. Although the Oxford vaporizer is practically fool-proof, frequent medical supervision is essential. On one occasion it was noticed that air could hardly be forced into the lungs. Below the inset rubber tube the cannula was blocked by inspissated mucus as suction had been omitted. To prevent a recurrence suction had to be carried out from then on at regular intervals whether mucus was present or not. Another time the original valve of the Oxford vaporizer—which has to be kept screwed down—had opened through friction against the bed-clothes, with the effect that most of the air did not reach the patient but escaped through the valve. It is preferable to remove the expiratory valve and to connect the rubber tubing direct to the Salt valve.

The Cardiff valve will no doubt replace the Salt valve, as only one hand is needed for inflation, and it will then be so easy to work the bellows that unskilled personnel can be employed.

The question is bound to arise whether manual or automatic inflation is preferable. It seems that both have their advantages and their drawbacks. During extensive epidemics, when many cases are gathered in one hospital, an automatic device will be very useful. It will save personnel and their training. Constant volume and speed of automatic inflation might be an advantage over manual inflation, which is bound to vary in intensity. Medical supervision can be carried out constantly in a large institution; experts are there to regulate volume, speed, and pressure of the machines, technicians can be called upon to adjust or repair them, and compressed air or nitrogen-oxygen mixtures are easy to obtain. But the single case in a cottage hospital without all these facilities is probably served much better by the almost fool-proof combination of the Oxford inflating bellows with the Cardiff inflating valve. No adjustments or repairs are needed, air and an oxygen cylinder are always available. Should there be any resistance to inflation, and the person working the bellows has been forewarned of such an occurrence, no undue force would be applied which might cause damage, while a machine would continue with its set pressure unless a safety valve was fitted. The bellows unit is portable and can be taken to the patient's home if he cannot be moved. It seems advisable to fit all small country hospitals with such a unit, which can also be used for any other case requiring artificial respiration.

The second case indicates a way in which patients without tracheotomy can be taken out temporarily from the iron

lung for more thorough nursing, massage, or any other treatment which is difficult or impossible to carry out through its windows. Rovenstine and Strauss (1946) intubated, inflated, and anaesthetized a patient who had been kept in a Drinker respirator, in order to perform a caesarean section. Intubation has to be performed on the conscious patient under local analgesia, but his co-operation is easily obtained once the procedure and its necessity are explained to him. In these cases a cuffed endotracheal tube is essential, otherwise inflation will not provide the same degree of oxygenation as the iron lung. Any anaesthetic machine can be used for that purpose, delivering pure oxygen. For short periods this will not cause any harm to the patient and no arrangements are needed for adding air or nitrogen. If the apparatus used is not fitted with a non-rebreathing device like the Salt or the Cardiff valve, carbon dioxide absorption will have to be employed.

The Danish team has demonstrated the analogy between respiratory paralysis produced deliberately by the anaesthetist by means of a relaxant drug and the paralysis caused by the poliomyelitis virus. By transferring a technique applied every day in anaesthesia to the treatment of a pathological process with similar manifestations the same results are obtained—namely, to tide the patient over a period of respiratory paralysis by means of artificial inflation. The difference, apart from the additional complicating symptoms of poliomyelitis, lies in the length of time during which this inflation has to be carried out. Succinylcholine wears off after about five minutes, tubocurarine after forty-five minutes; Case 1 lasted for less than four days, but some of the Danish cases required inflation for more than three months.

Once the similarity of muscular relaxation during anaesthesia and of paralysis of poliomyelitis is realized more analogies become apparent. Case 2 could not be ventilated efficiently because of partial obstruction of the airway by the patient's tongue, a picture familiar to any anaesthetist but one that is outside the range of observation of a physician who has spent years dealing exclusively with the treatment of infectious diseases. Most likely there will be a number of cases in which insertion of an airway—covered with an analgesic ointment like cinchocaine—which keeps the tongue forward will greatly improve ventilation by the iron lung.

Collaboration between physician and anaesthetist in the treatment of respiratory paralysis of poliomyelitis has resulted in the saving of many lives during the Danish epidemic, and more can be saved, as Case 1 of this report has shown. In our age of increased specialization in medicine it may be worth while to contemplate that close connexions exist between fields apparently as unrelated as, in our instance, poliomyelitis and anaesthesia.

Summary

Successful positive-pressure inflation by means of the Oxford vaporizer in a case of bulbar respiratory paralysis of poliomyelitis is described.

A method is outlined, and its application described, showing how poliomyelitis patients whose respiration is paralysed can be taken out of the iron lung temporarily.

The analogy between deliberately produced muscular relaxation during anaesthesia and paralysis of poliomyelitis is pointed out.

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A PNEUMOFLATOR ATTACHMENT TO BOYLE'S MACHINE

BY

T. M. WILLIAMS, M.R.C.S., F.F.A.R.C.S., D.A.

The need for automatic mechanical devices for maintaining controlled respiration during anaesthesia has been fully discussed by Mushin and Rendell-Baker (1953, 1954). This apparatus is a further development of the prototype described previously in a preliminary report (Williams, 1952), and differs in certain important respects from other mechanical respirators.

The apparatus consists of a small device which can be attached to the outlet of any standard Boyle's machine. In principle, it converts the continuous flow of gases into an intermittent one so that Boyle's machine is made suitable for performing automatic rhythmical inflation of the lungs. The prototype has been in daily use for the past five years, and has proved useful and effective in over three thousand patients, many of whom were undergoing major thoracic procedures. The apparatus is really intended, however, for anaesthesia in general surgery in circumstances in which controlled respiration is thought desirable. It can be quickly brought into use for varying periods of time, and whenever the anaesthetist is called upon to set up a transfusion or otherwise attend to the apnoeic patient.

The attachment has the following salient points: (1) It forms an integral part of Boyle's machine, and is therefore immediately available for use. (2) Soda-lime is not required, so that trichlorethylene may be used to supplement the gases if necessary. (3) The motive power for operating the mechanism is provided by the compressed gases within the cylinders. It is therefore independent of electric motors and has no inherent risk of electrical failure or explosion. (4) A safety valve prevents lung pressures rising above approximately 30 cm. of water. (5) A built-in valve allows air to supplement the gas mixture if spontaneous respiration unexpectedly returns and the inspiratory demand is greater than the gas-flows supplied by the machine. (6) A small lever projects through the detachable lid of the apparatus, and its rhythmical movement provides both visual and audible evidence of function. When this lever is held in the inspiratory position the lungs may be kept inflated momentarily if so required by the surgeon. Periods of deflation of the lung are obtained by temporarily opening the normal expiratory valve at the facepiece. (7) The rate and depth of respiration can be varied between adequate limits by the use of two controls only.

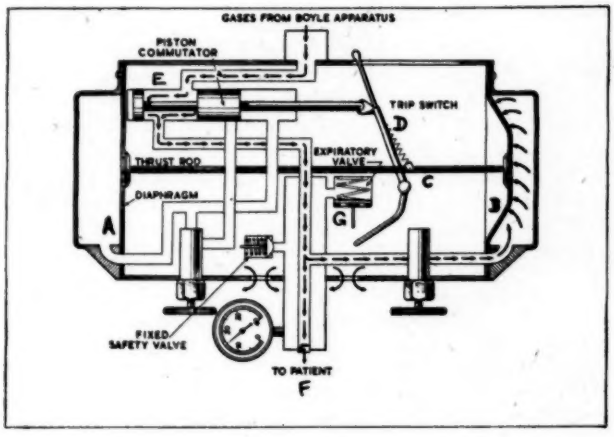
For efficient operation a flow of 15 litres a minute is required during the inspiratory phase. This is easily obtained from Boyle's machine, having an oxygen flowmeter graduated to give 5 litres a minute and a nitrous oxide flowmeter graduated to 10 litres. During expiration, however, the gas flow is cut off so that the actual consumption of gases is little more than half the above amount—that is, 8–9 litres a minute. In practice it is found that with continuous running a 20-cu. ft. (0.57 $m.^3$) cylinder of oxygen and a 200-gallon (910-litre) cylinder of nitrous oxide both last for approximately two and a quarter hours before depletion.

The gas mixture is delivered to the patient by means of a narrow-bore (3/16 in. (4.8 mm.) internal diameter) rubber tube which is attached to the apparatus by means

of a bayonet clip. It is brought through the bag mount and corrugated rebreathing tube to a point as near as possible to the patient. The diameter of this tube is important, and should not deviate greatly from this size, since the calibre of the tube determines to a large extent the minimal intrapulmonary pressure at which the machine will work. The corrugated tube is used for expiration only. This is by normal elastic recoil of lungs, the expired air passing up the corrugated tube and escaping through a large-bore expiratory valve within the attachment. Dead-space rebreathing is thereby reduced to a minimum by this unidirectional flow of the gases.

The Mechanism

The apparatus is provided with two stout diaphragms (A) and (B), which act alternately on the metal thrust rod (C). The lateral movement of this rod disturbs the balance of a trip switch (D), which thus moves instantly from one extreme position to the other. The piston commutator (E) is attached to this trip switch.



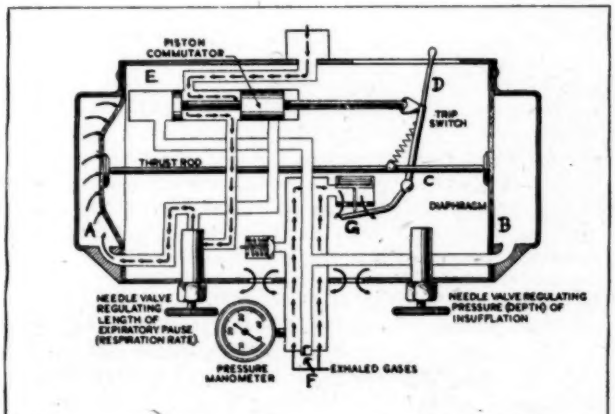


Diagram showing insufflation and exhalation phases.

During the inspiratory phase gases flow from the anaesthetic apparatus through the narrow tube (F) to inflate the patient's lungs. A small proportion of this flow, augmented by the rising intrapulmonary pressure, passes into the right-hand diaphragm chamber at a rate controllable by the right-hand needle valve, the setting of which determines the degree, or depth, of inflation. The pressure thus exerted on the diaphragm (B) gradually moves the thrust rod to the left until the trip switch flicks over into the expiratory position.

In the expiratory phase the gas supply to the patient is cut off by the valve (E), and the large-bore expiratory valve (G) is opened so that the expired gases can return along the corrugated tubing and out through this valve. Meanwhile a small gas-flow from the parent machine is allowed to enter the left-hand diaphragm chamber at a rate controllable by the left-hand needle valve, which thereby determines the length of the expiratory pause. When the thrust rod has moved sufficiently to the right the sudden movement of the trip switch closes the expiratory valve abruptly, so completing the respiratory cycle. The expiratory valve is fitted with a light spring, and if a deep inspiration should unexpectedly occur the valve opens freely, allowing air to supplement the gas-flows.

Clinical Use

When controlled respiration is desired the apparatus is brought into use in the following way. The oxygen flow is increased to 5 litres a minute and the nitrous oxide to 10 litres. The sliding clip which secures the manual control lever is released, and the bag-mount lever turned off so that the reservoir bag no longer communicates with the corrugated tube. The expiratory valve at the facepiece is closed and the cuff of the endotracheal tube inflated so that gas leakage is reduced to a minimum.

The automatic action now begins, and the right-hand control should be used in conjunction with the manometer to adjust intrapulmonary pressures to the desired level. The left-hand control is then adjusted to allow a suitable expiratory pause; this should be at least as long as the time taken for inspiration (Watrous *et al.*, 1950, 1951).

When the pneumoflator is in operation a soft "click" is heard for each phase of respiration. There is also a jerking or oscillatory movement of the rotameter bobbins. This is a normal accompaniment of efficient working, and gives further evidence that cylinder pressures are adequate. During the past five years the bobbins on our machines do not appear to have been adversely affected by this movement. Occasionally a small adjustment to the calibration of the manometer may become necessary. This is accomplished when the attachment is out of use by turning the milled edge of the dial until a zero reading is obtained.

Since soda-lime is not used with this attachment, trichlorethylene can be used intermittently at any time during the operation if it becomes necessary to deepen the anaesthesia. It is essential that the cork washer between the trichlorethylene bottle and its control head be intact, as a gas leak here prevents the apparatus working efficiently.

If at any time the anaesthetist wishes to change to manual control of respiration, or if natural breathing is returning and is desired, the apparatus is put out of action by opening the reservoir-bag mount and expiratory valve. The manual control lever is secured in the inspiratory position, and the gas-flows are then reduced once more to the normal limits for Boyle's machine.

Inflation Pressures

So many factors influence the choice of intrapulmonary pressures during controlled respiration that no hard-and-fast rule can be given. The reader is advised to study the many interesting discussions on this elsewhere (Slocum *et al.*, 1950; Mushin and Rendell-Baker, 1953).

With this pneumoflator, however, pressure up to 30 cm. of water may be used, but generally it is found that 12–20 cm. of water pressure is sufficient for the average adult lying on a level table. A guide to a suitable pressure is obtained by squeezing the reservoir bag by hand for a few moments before bringing the apparatus into use. The experienced anaesthetist can tell when he is performing efficient ventilation by the feel of the bag. The pressure on the manometer is noted and the pneumoflator set to work at this figure.

Conclusion

A machine is no more than a tool in the hands of the operator. Only the anaesthetist can fully assess the unique information which manual compression of the rebreathing bag can give. But with the present widespread

use of the various muscle relaxants, and the severity of many surgical procedures, an automatic breathing device can be of the greatest value during periods of respiratory depression. It allows the anaesthetist both greater mobility and the freedom of his hands to attend to the general care and welfare of his patient.

I wish to thank Dr. H. Duncan Davies, medical superintendent, Morriston Hospital, and the surgical staff, both past and present, for their very kind co-operation during the development of this apparatus; Professor W. W. Mushin, Cardiff, for his invaluable advice and guidance; and Mr. Elwyn Williams, S.R.N., charge nurse to the anaesthetic department, for his most valued assistance. I am also grateful to Mr. A. Charles King, who before his retirement gave such whole-hearted encouragement, and to Mr. A. J. Juby, of Messrs. A. Charles King Ltd., for his practical suggestions and courtesy.

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ACQUIRED AFIBRINOGENAEMIA COMPLICATING PREGNANCY

REPORT OF TWO CASES OF CONCEALED ACCIDENTAL HAEMORRHAGE TREATED BY HUMAN FIBRINOGEN

BY

VIVIAN H. BARNETT, M.B., F.R.C.S., M.R.C.O.G.
Consultant Gynaecologist and Obstetrician

AND

C. A. CUSSEN, M.B., M.A.O., D.G.O.
Registrar

(Royal Salop Infirmary and Copthorne Hospital, Shrewsbury)

Afibrinogenaemia is a condition in which the blood is rendered incoagulable owing to the absence of one of the principal components of the normal blood-clotting mechanism. DeLee (1901) first described this condition in pregnancy when he referred to a haemophilia-like phenomenon complicating two of his cases. Williams (1925) reported a case in which bleeding continued for twelve hours after delivery, despite a well-contracted uterus and in the absence of any detectable traumatic lesion. Davis and McGee (1931) cited two fatal cases in which packing of the uterus and clamping of the uterine arteries failed to control haemorrhage. Dieckmann (1936) first suggested the true nature of the condition—a lack of circulating fibrinogen—and reported two cases of his own in which, in addition to uterine bleeding, there was haemorrhage from the gums and stomach and into the subcutaneous tissues. Tagnon *et al.* (1946) described a fatal case of post-partum haemorrhage in which the patient's blood was incoagulable, but clotted when fibrinogen was added to a freshly collected specimen. Weiner *et al.* (1950) reported three cases of defective coagulation mechanism in patients displaying evidence of rhesus incompatibility during their pregnancies.

Coagulation Reaction

The essential reaction in coagulation of the blood is the conversion of the soluble protein fibrinogen into the insoluble protein fibrin by means of the enzyme thrombin. Fibrinogen is a protein of high molecular weight and exists in the circulating blood as such. It is probably formed in the liver, and damage to this organ results in a rapid fall in the plasma fibrinogen concentration. This indicates that the circulating fibrinogen is rapidly destroyed or utilized by the body, but the manner of destruction or of utilization is unknown. Thrombin, an albumin, is not present in the circulating blood, but is formed from its inactive precursor prothrombin when blood is shed. Prothrombin, a globulin, is formed in the liver, and its synthesis is dependent upon an adequate supply of vitamin K. For the activation of prothrombin, free calcium ions and certain organic activators of obscure composition named thromboplastins are necessary. These thromboplastins are derived from damaged tissues, from disintegrating blood platelets, or from the plasma itself. The normal blood-clotting mechanism can be simply outlined thus:

$$\left.\begin{array}{l}\text{Prothrombin}\\ +\\ \text{Free calcium}\\ +\\ \text{Thromboplastins}\end{array}\right\} = \text{Thrombin} + \text{Fibrinogen} = \text{Fibrin}$$

All authorities are agreed that the essential factor in the incoagulability of the blood is a lack of circulating fibrinogen. The aetiology of the afibrinogenaemia, however, remains speculative. Willson (1922) suggested that a toxin which he named "haemorrhagin" was responsible for the interference with the normal blood-coagulation mechanism. In 1929 Sakurai succeeded in defibrinating blood in experimental animals by injections of placental extracts, and in 1936 Eley *et al.* confirmed the antihaemophilic activity of these extracts and in addition produced evidence of intravascular coagulation in guinea-pigs and monkeys. Howell (1941) made a valuable contribution when he showed that injections of thromboplastins resulted in depletion of the blood fibrinogen and rendered the blood incoagulable. Furthermore, he suggested that these substances were liberated into the maternal circulation in cases manifesting the haemorrhagic diathesis following abruptio placentae.

Schneider (1947) concluded, following extensive experiments, that thromboplastins were in fact the toxic elements which, when liberated into the blood stream, resulted in afibrinogenaemia. Reid (1951) suggested that a fibrolytic enzyme (first referred to by Tagnon *et al.* in 1946) was responsible for the depletion of fibrinogen. He states that this enzyme is normally present in the circulating blood, but that its activity is held in abeyance by an antifibrolytic substance and it is liberated in excessive amounts only in cases of shock or haemorrhage. An antithrombin substance (Ratnoff and Vosburgh, 1952) has also been cited as the cause of the haemorrhagic diathesis; this, however, would appear to be unlikely, as antithrombin does not cause a depletion of fibrinogen—a constant biochemical finding. However, it may well be that the production of antithrombin is of secondary importance in producing defective haemostasis, as suggested by Weiner *et al.* (1953). Liver damage has also been suggested as the underlying cause of the afibrinogenaemia, but necropsy examination has failed to show any evidence of hepatic insufficiency.

The Thromboplastin Theory

However, the consensus of opinion undoubtedly favours the "thromboplastin theory," and it would appear from a survey of the literature that it is most acceptable.

Thromboplastins, as stated above, are substances of obscure composition. They are a normal component of all tissues, but some tissues contain a higher concentration than others. The uterus, placenta, lung, and brain are known to contain large quantities.

Reid *et al.* (1953), following up previous experiments by Steiner and Lushbaugh (1951), confirmed that amniotic fluid emboli can occur during pregnancy. Furthermore, they ascertained that amniotic fluid is a rich source of thromboplastins, which it derives normally from foetal exfoliation. In addition, the thromboplastin content of the amniotic fluid is greatly enriched from the decidua.

In pregnancies in which there is premature separation of the placenta (abruptio placentae) it has been shown by Schneider (1952) that rupture of the basal decidual plate occurs, resulting in the liberation of thromboplastins into the maternal circulation.

Weiner *et al.* (1950) reported that afibrinogenaemia may develop in an occasional Rh-negative patient in which the foetus has died and is retained *in utero*. They suggest that in these cases the most likely cause of the incoagulability of the blood is resultant on the death of the foetus; its membranes and the decidua disintegrate and allow the absorption of thromboplastins into the maternal circulation.

To summarize, therefore, the present hypothesis of afibrinogenaemia is as follows: thromboplastins are liberated from the uterus or its contents and gain access to the maternal circulation, where they set in motion the normal blood coagulation mechanism, resulting in extensive intravascular clotting. Consequent on this there is a marked depletion of the circulating fibrinogen, and the liver is unable to make good the deficiency in time to prevent the haemorrhagic diathesis manifesting itself.

It is suggested that a fibrolysin is produced in the maternal blood as a counter-measure to combat the intravascular deposition of fibrin, and that this in turn aggravates the condition rather than alleviating it, by producing fibrin emboli (see below).

Conditions Associated with Afibrinogenaemia

Clinically, so far as is known, afibrinogenaemia may manifest itself in three conditions complicating pregnancy: (1) abruptio placentae; (2) amniotic fluid embolism syndrome (Reid *et al.*, 1953); and (3) rhesus incompatibility resulting in intrauterine death and retention of the foetus *in utero* (Weiner *et al.*, 1950). In these conditions, if depletion of the fibrinogen has taken place, the patient's blood fails to clot, and haemorrhage, uncontrollable by ordinary measures, will take place from any raw surface—that is, placental site or episiotomy incision. This is illustrated by the cases reported here, in which, despite a well-contracted uterus and the absence of any apparent traumatic lesion, uterine bleeding continued unabated and the blood which was shed failed to clot.

Bleeding may even occur from the intact mucous membranes and subperitoneally; these latter are frequently apparent at caesarean sections performed on cases of abruptio placentae, and constitute the classical Couvelaire lesions. According to A. P. Barry and to K. Feeney (personal communications), these internal haemorrhages are one of the chief causes of death in accidental haemorrhage.

The internal haemorrhagic manifestations are explained by (1) the ischaemic necrosis of the small vessels due to fibrin emboli resulting from the action of fibrolytic enzymes on the intravascular deposits of fibrin; and (2) the associated incoagulability of the blood.

The diagnosis of the condition is not difficult in the established case. Purpura haemorrhagica may simulate the condition, but can be distinguished by the fact that the blood-coagulation time is normal and bleeding does not characteristically come from the uterus but rather from lacerations of the cervix, vagina, or perineum. Obvious traumatic causes of haemorrhage must, of course, be excluded by vaginal examination. Rupture of the uterus is more difficult to exclude without laparotomy; but the nature of the labour and delivery will suggest whether or not its possibility should be seriously considered, and any blood issuing from the vagina will be seen to clot in the container. Absolute diagnosis of afibrinogenaemia can only be made biochemically, a method which will show the depletion or absence of fibrinogen. The condition should always be kept in mind when dealing with cases of abruptio placentae, with retention of a dead foetus *in utero* or with premature rupture of membranes. Potential and established cases can be detected by the "clot observation test" (W. Weiner, 1953, personal communication).

Treatment

The treatment of the condition falls under two headings: prophylaxis and established cases.

Prophylaxis.—This is directed towards early detection and prompt correction of the afibrinogenaemia. In the three varieties of cases already outlined, but chiefly in cases of abruptio placentae—for these are most likely to manifest the haemorrhagic diathesis—the possibility of the complication of incoagulability of the blood must be borne in mind. Blood should be drawn from any suitable vein, and Weiner's "clot observation test" be carried out at hourly intervals. When the fibrinogen concentration of the blood has decreased to a critical level the blood withdrawn from the vein will fail to coagulate; when the fibrinogen level falls to a lesser degree clotting-time will be delayed beyond the normal maximum of ten minutes, and when it does occur the coagulum will fragment and dissolve within one hour when kept at a temperature of 38° C.

Determination of the blood fibrinogen level may be carried out, where facilities are available, when the "clot observation test" indicates a defective clotting mechanism. The normal fibrinogen content of the blood varies between 190 and 330 mg. per ml. The minimal level for haemostasis is considered to be 100 mg. per ml. (Reid, 1951). When the findings suggest a fall or depletion of the fibrinogen, immediate replacement must be made by intravenous administration of human fibrinogen. The amount of replacement required depends upon the clotting behaviour of the blood as displayed by the "clot observation test." In cases of abruptio placentae blood transfusion should also be begun, to counter the shock which will undoubtedly manifest itself owing to the concealed loss of blood (O'Donel Browne, 1952).

Established Cases.—Moloney *et al.* (1949) were the first to treat successfully an established case by combining fibrinogen replacement and blood transfusion. In these cases the patient manifests varying degrees of shock, depending on the amount of internal and external blood loss. Therefore, in addition to correcting the afibrinogenaemia, antishock therapy must be immediately started. Restoration of blood volume is of prime importance, but it must be clearly understood that the condition cannot be corrected by multiple transfusions of stored blood alone. The amount of fibrinogen required in established cases is still debatable; it has, however, been established that between 8 and 12 g. of fibrinogen is present in the blood of a normal person; therefore theoretically in a case of complete defibrinogenation an equivalent amount should be given intravenously. Reid (1951) suggested that the initial dose of fibrinogen should be 4 to 6 g., and that repeated injections of 1 g. at half-hourly intervals should be given until the blood-clotting mechanism has returned to normal. Moore (1954) has successfully treated a case of afibrinogenaemia associated with abruptio placentae by the administration of human fibrinogen (2 g.) and transfusions of whole fresh blood. However, in our opinion far smaller doses of fibrinogen are effective, as illustrated in the cases presented, and we agree with Weiner that there is no doubt that fibrinogen is the most effective therapeutic agent in the cure of these cases.

Case 1

A 33-year-old 7-gravida, whose estimated date of delivery was October 25, 1953, had maintained excellent health during her pregnancy except for a moderate degree of pyelitis at the eighth month, which responded to chemotherapy. Her past and family histories were free of any evidence of abnormal bleeding tendency. Her previous

pregnancies were uneventful and the blood loss in the third stage had always been within normal limits.

The patient was admitted to hospital at 2.15 a.m. on October 23 as a case of abruptio placentae. She gave a history of having had continuous abdominal discomfort for five hours and slight vaginal bleeding for two hours before admission. Foetal movements had not been appreciable since the onset of vaginal bleeding. Labour had begun on the way to hospital, and the membranes had ruptured immediately before admission.

On examination her general condition was good, the pulse rate 84 a minute and of good volume, temperature 97.8° F. (36.6° C.), and blood pressure 115/70. There was no oedema or albuminuria. The uterus corresponded in size to the period of gestation; it was tense and tender on palpation, but not markedly so. Foetal parts were difficult to define clearly, but the lie was longitudinal, with the back on the left side and the head engaged in the pelvis. The foetal heart was not heard. There was a slight amount of dark non-clotting blood coming from the vagina; a rectal examination showed the presenting part to be at the level of the ischial spines, and the cervix to be three-quarters dilated. The patient was in labour.

She had a spontaneous delivery of a full-term stillborn male infant at 3 a.m., and the placenta together with 1 pint (570 ml.) of old blood clot was immediately expressed from the uterus. Ergometrine, 0.5 mg., was given intramuscularly and the uterus contracted firmly. There was no perineal tear, nor was episiotomy necessary. The placenta, when examined, displayed all the typical findings associated with accidental haemorrhage. Immediately after delivery the patient's condition was good, pulse rate 92 and blood pressure 120/70.

After the delivery there was a very slight blood loss per vaginam despite a well-contracted uterus; the midwife in charge was not worried, regarding the loss as being within normal limits. At 3.55 a.m. she became anxious owing to the persistence of the slight bleeding, which now amounted to 1 pint (570 ml.). The patient's pulse rate was 105 and thready, the blood pressure was 95/45, and, in addition, her colour was pale and her skin clammy. It was observed that the blood which was shed failed completely to coagulate in the container.

An intravenous drip of "plasmosan" was begun at 4.5 a.m. and arrangements were made for immediate cross-matching of the patient's blood. A speculum examination failed to reveal any apparent traumatic lesion. In view of this and the incoagulability of the blood passed per vaginam, a definite diagnosis of afibrinogenaemia was made. Dr. Weiner, of the Birmingham Transfusion Service, was contacted, and he kindly provided a supply of fibrinogen. At 4.20 a.m. blood was substituted for the plasmosan.

Despite rapid blood transfusion the patient's condition continued to deteriorate, and the vaginal bleeding persisted. At 5.55 a.m. the fourth pint of blood was started, and the apparent blood loss up to that time was measured at 5 pints (2.8 litres). The pulse rate was 115; its volume was weak but was regular; the blood pressure was 90/40.

At 6.5 a.m. 20 ml. of human fibrinogen (404 mg.) was administered intravenously, and the vaginal bleeding ceased at 6.25 a.m. The patient's condition improved rapidly thereafter; in fact, the improvement was more rapid than one would expect from cessation of the external bleeding alone.

From this time the patient's condition continued to improve. A total of 6 pints (3.4 litres) of blood was transfused, and there was no recurrence of the bleeding. The puerperium was apyrexial, the uterus involuted normally, and the patient was allowed out of bed on the second day, being discharged home on the tenth day.

Blood which was collected from the patient during the "bleeding phase" failed to coagulate while under observation for 48 hours, and the pathological report on it was as follows: "Serum prothrombin time, 5 minutes +; tiny ill-formed clot at 100 seconds (normal control, 24 seconds). Plasma prothrombin time, 30 minutes + (normal control, 14 seconds). Microelectrophoresis of plasma shows absence of fibrinogen bands. Twelve hours later, after administration of the fibrinogen, clotting and bleeding times were normal and platelets were seen in a film to be present, but appeared large in size and reduced in numbers; count, 120,000 per c.mm."

The pathological report on the blood on October 25 was as follows: "Serum prothrombin time, 30 seconds (normal control, 11 seconds); plasma prothrombin time, 11 seconds (normal control, 11 seconds). Therefore prothrombin consumption was within normal limits. Microelectrophoresis of plasma shows fibrinogen band to be present, but in much reduced proportion. Bleeding-time, 6 minutes, clotting-time (Lee and White's method), 6 minutes (normal, 6 to 15 minutes); clot retraction, normal; platelets (film), within normal limits."

Case 2

A 37-year-old 6-gravida whose expected date of delivery was June 19, 1954, had been in good health throughout her present pregnancy, and had been seen antenatally by her general practitioner and the district nurse. Her past and family histories were free of any evidence of abnormal bleeding tendency. All her previous pregnancies and labours had been normal, the last having taken place in 1947.

The patient was admitted on May 1, at the thirty-third week of pregnancy, having a history of accidental antepartum haemorrhage, with considerable external blood loss. She was sent in by her own doctor from an outlying district, and was seen by us at 6 p.m. The following were the findings. Oedema of ankles; albuminuria ++; blood pressure, 120/70; tense tender uterus; foetal parts very difficult to determine with accuracy; vertex presentation; foetal heart inaudible; brisk haemorrhage per vaginam; catheter urine ½ oz. (14 ml.).

6.20 p.m.: Clot observation test demonstrated incoagulability, and subsequent micro-electrophoresis showed absence of fibrinogen bands. 6.30 p.m.: Blood transfusion started. 7.30 p.m.: Fibrinogen, 0.13 g., obtained from Birmingham, was given intravenously. 8 p.m.: Test demonstrated clotting; the membranes ruptured surgically; 2.5 units of "pitocin" injected. 8.30 p.m.: 2.5 units of pitocin injected. 9 p.m.: Labour started; blood pressure, 130/75. 11.45 p.m.: Spontaneous delivery of a dead foetus was followed immediately by delivery of the placenta. There was evidence of abundant retroplacental bleeding having taken place previously.

The immediate post-partum bleeding amounted to 24 oz. (680 ml.), and, despite a well-contracted uterus and absence of trauma, uterine bleeding continued. The blood was obviously incoagulable; blood pressure, 115/60.

May 2.—12.20 a.m.: A further 0.13 g. of fibrinogen was given (second dose). 1 a.m.: Test again showed clot formation. A catheter specimen of urine taken at this time showed marked haematuria. The total amount of catheter urine collected between 6 p.m. of the day of admission (not including the first catheterization) and 1 a.m. was 5 oz. (140 ml.). 1.30 a.m.: Blood loss now much less, but coagulation still entirely absent. 5 pints (2.8 litres) of blood had now been given by transfusion. 2 a.m.: Blood loss slight, but no evidence of coagulation yet seen; blood pressure, 104/60. 2.45 a.m.: 0.13 g. of fibrinogen given (third dose); blood loss still slight, but continuous and without clot formation. 3.15 a.m.: Blood loss ceased entirely. Clot rapidly formed. Six pints (3.4 litres) of blood had now been given by transfusion; blood pressure, 140/90. Total urinary output since 6 p.m. on the day of admission was 8½ oz. (240 ml.).

The subsequent recovery of the patient was uneventful.

Summary and Conclusions

The suggestion that internal haemorrhage might be dependent on a defect in the clotting mechanism of the blood was first made when DeLee described a haemo-

philia-like phenomenon complicating accidental ante-partum haemorrhage. Dieckmann first suggested the true nature of this condition—a lack of circulating fibrinogen.

The essential reactions in blood coagulation are described, and shown in diagrammatic form.

Every case of accidental ante-partum haemorrhage must be suspected of internal haemorrhage, which can prove fatal; and the possibility of a severe post-partum bleeding, uncontrollable by ordinary means due to blood incoagulability, must also be kept in mind.

The clot observation test as described by Weiner in 1953, carried out at hourly intervals, gives clear warning of developing fibrinogen deficiency with all its dangers, and enables treatment to be given at an early stage when the prognosis is good.

The administration of pure human fibrinogen is essential, should severe afibrinogenaemia develop, if life is to be saved. The administration of whole fresh blood, although it contains fibrinogen, is by no means as efficient, since it is not possible to give the fibrinogen it contains quickly enough to prevent the rapid conversion of the latter to fibrin.

We wish to thank Dr. G. H. Grant and Dr. M. Symons, of the Donaldson-Hudson Pathological Laboratory, Royal Salop Infirmary, for their valuable help in the blood investigations of these cases; Dr. W. Weiner, Director of the Regional Transfusion Centre, for the supply of fibrinogen. We are also grateful to Dr. Alan Browne, of the Rotunda Hospital; Dr. A. Barry, Master of the National Maternity Hospital, Dublin; and Dr. Kevin Feeney, Master of the Coombe Lying-in Hospital, Dublin, for their interest and advice; and to Mrs. M. Roberts, of the Royal Salop Infirmary, for her willing co-operation in the preparation of this communication.

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The Universities Federation for Animal Welfare, in association with the Animal Welfare Institute of New York, has appointed Dr. W. M. S. RUSSELL, D.Phil., as Research Fellow to study the history and progress of the introduction of humane techniques into experimentation on animals, with a view to assisting further progress. Examples of progress already achieved are the use of anaesthetics in experiments involving operations, the reduction of the requisite number of animals by means of modern small-sample statistical theory, and in the assay of drugs the substitution of painless (e.g., chemical) criteria for various criteria entailing discomfort.

THE NATURE OF BELL'S PALSY

BY

R. WYBURN-MASON, M.A., M.D.

The anterior primary divisions of the second and third cervical nerve roots divide into two and the adjacent parts of each root join to form the great auricular, lesser occipital, and cutaneous cervical nerves beneath the sternomastoid muscle. The latter appear at the mid-point of the posterior border of the muscle, where they pierce the deep fascia, usually immediately above and behind the external jugular vein, which crosses the posterior border of the muscle at the same point. The great auricular nerve then ascends towards the lobe of the ear, crossing the muscle obliquely, and, as it does so, divides into anterior and posterior branches. The posterior branch joins the posterior auricular branch of the facial nerve behind the ear, communicates with the lesser occipital nerve and the auricular branch of the vagus, and supplies the skin over the mastoid process. The anterior branch unites with the various branches of the facial nerve as they lie on and within the substance of the parotid gland. Other branches supply the lobe of the ear, part of the posterior and lower part of the auricle, and the skin over the angle of the jaw and parotid gland. The great auricular nerve is purely sensory and some of its fibres join the facial nerve and with it pass to all parts of the face. The above facts and the procedure for alcohol block and section of the great auricular nerve have been previously described (Wyburn-Mason, 1953).

Some Causes of Lower-motor-neurone Facial Palsy

A lower-motor-neurone lesion of the facial nerve may be produced in many ways. I am not here considering cases in which the facial palsy is due to an intracranial lesion, to disease or fracture of the petrous bone, or to middle-ear disease, but only those due to certain infratemporal causes. A palsy arising for no apparent cause is usually given the term Bell's palsy, but one with identical features may be produced in a number of ways, of which the following are of interest.

(a) Facial Palsy and Zoster of the Second and Third Cervical Dermatomes

Cases of herpes zoster of C 2 and 3 zonal areas, of the trigeminal area, or of so-called "otic zoster" are not infrequently complicated by a facial weakness similar to that occurring in cases of Bell's palsy (see Case 1), which may be transient or permanent. As shown by Lewis (1927), "herpetic and herpetiform eruptions occur as sequels to lesions of the sensory nerve tracts; not only do they follow irritative lesions of the [root] ganglion, but they are produced also by lesions of those tracts distal to the ganglia themselves." Such irritation of nerve roots or their branches may follow mechanical, physical, or chemical trauma, gunshot wounds, *x*-irradiation, primary or metastatic tumours, or handling of the nerve roots at operation. The irritation causes the passage of antidromic impulses peripherally. These liberate histamine (or H-substance) and possibly acetylcholine (Grant, Pearson, and Comeau, 1936), and they cause not only vasodilatation, but exudation of fluid from the blood vessels, leading to oedema, small haemorrhages, and also the signs of inflammation (see Lewis, 1927). The inflammatory changes are found in the skin and subcutaneous tissues and also in deeper tissues and their contained structures. When C 2 and 3 nerve roots are irritated, giving rise to herpes zoster in the affected skin segments, the antidromic impulses pass peripherally in those fibres (among

others) which form the great auricular nerve. Some of its fibres join the facial nerve in the region of the parotid gland. This nerve, like other tissues in the neighbourhood of the branches of the irritated nerve roots, must become swollen and exhibit inflammatory changes. The following observation was made on such a case.

Case 1.—Two weeks previous to examination a man aged 41 developed pain in the right side of the face, forehead, temple, ear, and down the side of the neck. Three days later a typical zosteric eruption appeared just behind the right ear extending on to the medial side of the pinna, on the temple above the ear, and on the chin downwards to the front of the neck (see Diagram). The eruption on and behind the pinna and on the temple was in the distribution of the great auricular and that on the chin in the distribution of the cutaneous cervical nerves. Eleven days after the onset of pain (three days before examination) he developed a right-sided facial palsy.

Examination showed the presence of a complete right-sided lower-motor-neurone facial weakness, loss of taste on the right side of the anterior two-thirds of the tongue, and a zosteric eruption in the areas shown. Alcohol block of the great auricular nerve produced severe pain in the region where pain was already present in the face, ear, and temple. At the end of seven days he was seen again, when the lesions behind and above the ear were now almost healed, but that on the chin was weeping and painful. He had had no pain in the areas around and above the ear since the injection. There was a remarkable improvement in the facial weakness. He was seen again after another week, when the facial movements and taste sensibility had returned, but the herpetic eruption of the chin was still sore and weeping. That on, above, and behind the ear had now healed and was quite painless.

This procedure has been carried out in three other similar cases with the same results. These observations show that interruption of the antidromic impulses in the great auricular nerve heals both the skin lesions and facial palsy. It would seem, therefore, that in such cases the origin of the facial palsy might well be the extension of the inflammatory changes in the great auricular nerve into the facial nerve.

(b) Association with Tic Douloureux

I have put forward evidence to show that in a large proportion of cases of tic douloureux the pain is due to a disturbance of the great auricular nerve (Wyburn-Mason, 1953). Tic douloureux may be associated with facial palsy and spasm (Harris, 1937), suggesting that both conditions are due to the same underlying cause—a lesion of the great auricular nerve.

(c) Facial Palsy with Gunshot Wounds of the Great Auricular Nerve

Gunshot wounds involving the region of the upper part of the sternomastoid muscle may irritate the great auricular nerve, giving rise to a traumatic neuritis. Such wounds may be complicated by a transient facial palsy, even though the facial nerve is not directly injured. Case 2 illustrates such a sequence of events.

Case 2.—A man aged 25 was wounded in action by a small piece of shrapnel about ¼ in. (6 mm.) long, which penetrated the left side of the neck about 1½ in. (3.8 cm.) below the lobe of the ear to come to rest within the sternomastoid muscle. He immediately suffered from intense vertigo. The metal was removed at operation that day, and the wound healed by first intention. Next day he complained of intense left-sided hemicrania extending into the face, frontal, temporal, and occipital regions. Two weeks later, when the wound had practically healed, a lower-motor-neurone facial weakness developed. The symptoms diminished in severity over the next two or three months, but since that time he had been subject to almost daily left-sided hemicrania, especially in hot atmospheres, on bending, or in damp weather. When examined some three years after injury, a scar was present over the upper part of the left sternomastoid muscle, pressure on which caused an intensely unpleasant pain to shoot up into the ear, temple, and face. Taste sensation was normal. No sensory loss was found. There were some mass movements and spasm on attempted movement of the left side of the face and delay in eye closure on this side.

The site of the injury, the distribution of the pain after it, and the reference of pain on pressure over the scar in this case make it likely that the great auricular nerve was damaged. On the other hand, the site of the injury was some distance away from the facial nerve, and the facial weakness did not appear for some time after the wound or operation and when healing had taken place, suggesting neither the wound nor operative trauma had injured the facial nerve directly. A great auricular neuritis would again seem to have preceded the development of the facial palsy.

(d) Facial Palsy from X-irradiation Over the Great Auricular Nerve

X-irradiation produces inflammatory changes in the tissues through which it passes. It is not infrequently carried out over the upper part of the sterno-mastoid muscle (on which lies the great auricular nerve) in cases of malignant disease of the underlying glands or of the larynx and pharynx. I have observed seven cases in which this has been followed by a lower-motor-neurone facial palsy. Case 3 is an example of this sequence of events.

Case 3.—A man aged 60 had for six months noticed a lump on the right side of the tongue. Examination revealed leucoplakia of the tongue and a large nodular ulcerating growth of the whole right side of that organ and involving the left side of the under surface. An enlarged lymph node was present in the left upper deep cervical group. Biopsy of the mass revealed a squamous-cell carcinoma. He was treated with teleradium to the tongue and both sides of the neck. During and following this he developed severe dull aching pain in the ear and temporal region passing into the side of the face, eye, angle of the jaw, and back of the neck on the right side. One month after cessation of treatment a right lower-motor-neurone facial palsy appeared.

Examination showed no evidence of the primary growth. A complete right-sided lower-motor-neurone facial weakness was present. Taste could not be tested. There was no superficial sensory loss in the trigeminal area. Acute tenderness occurred on pressure over the nerves of the right cervical plexus, which caused pain to shoot up behind the ear and into the face and occipital region. Injection of 2 ml. of 2% procaine into the great auricular and lesser occipital nerves relieved the pain completely for several hours. Later, 2 ml. of absolute alcohol was injected in the same region, the symptoms being partly relieved for three weeks. They then returned as before, and the injection was repeated with the same effect, but symptoms again returned. After a third injection pain was completely relieved for about four months. There was a gradual improvement in the facial weakness.

These observations show that a great auricular and lesser occipital neuritis existed in this case, and was associated with a facial palsy.

(e) Facial Palsy from Alcohol Irritation of the Great Auricular Nerve

For a number of conditions, including frontal headache, I have carried out alcohol block of the great auricular nerve (Wyburn-Mason, 1953). Occasionally the initial attempt to infiltrate the nerve has not succeeded in interrupting its fibres, but has only caused their irritation. In three such cases this has resulted in a transient Bell's palsy on the affected side and the weakness has given way to mild transient facial spasm.

(f) Facial Palsy from Fracture of the Odontoid Process of the Axis

Fracture of the odontoid process of the axis vertebra may result in irritation of the second and third cervical nerve roots, which lie above and below the vertebra, and when this occurs the accident may be complicated by a transient facial palsy as in Case 4.

Case 4.—A man aged 28 received a blow on the back of the neck with a rifle butt. He felt a crack in his neck and was immediately seized with severe pain and a sensation of pressure and tingling in the occipital region and vertex. The pain spread into the face, throat, and ears. He was nauseated and vomited,

had severe vertigo and tinnitus, and felt deaf. He was admitted to hospital, where *x*-ray films revealed a fracture across the base of the odontoid process of the axis. Next morning he developed a left-sided Bell's palsy. His neck was put in a plaster collar, in which he remained for several months. During this time the head pains improved somewhat, and there was a gradual improvement in the facial weakness.

Such irritation of the nerve roots causes inflammation in the second cervical nerve root, which sends fibres into the great auricular nerve. Once again a traumatic neuritis affecting the fibres of the great auricular nerve preceded the onset of facial palsy.

(g) Facial Palsy from Lesions of the Upper Cervical Cord Segments

Lesions of the upper segments of the cervical cord, including high cervical tumours compressing the cord from without, which perhaps also irritate the upper cervical nerve roots, may be complicated by a facial palsy of lower-motor-neurone type (see Symonds and Meadows, 1937). This may occur even when there exists no traction on the medulla and even when there is no extension of the growth through the foramen magnum to involve the roots of the more caudal cranial nerves. Case 5 is an example.

Case 5.—A man aged 27 had for four years noticed a numbness of the left side of the neck and face, followed by progressive weakness of the left hand and arm and stiffness and weakness of the legs, especially the left. On his admission to hospital, the cerebrospinal fluid was found to contain 200 mg. of protein per 100 ml. and Queckenstedt's test showed a block in the circulation of the fluid. The Wassermann reaction was negative in fluid and blood. Laminectomy, carried out at the level of C 2, 3, and 4 vertebrae, revealed a spindle-like swelling of the cord due to a tumour extending down to the middle cervical region, probably C 5 segment, and upwards to the first cervical segment. The cord was incised posteriorly in the midline and tumour tissue welled up. Sections showed it to be a glioblastoma multiforme.

On examination six weeks after operation the positive findings were left-sided Horner's syndrome; left lower-motor-neurone facial weakness; wasting of the left side of the tongue, trapezius, and sternomastoid muscles, and weakness of the left side of the palate; taste sensation normal; impairment of all forms of superficial sensation over the whole of the left side of the body reaching up to the level of and including C 3 segment. The left arm was spastic, held flexed across the chest, and its tendon reflexes were very brisk. Crepitus and arthritis of the shoulder-joints, neck, elbow, and wrist were present, more marked on the right side. There was severe wasting of the muscles of the left upper arm, rhomboids, upper trapezius, and sternomastoid. The right leg was slightly spastic, the left more so. The tendon reflexes in the lower limbs were brisk, especially on the left. The plantar reflexes were extensor and the abdominals were absent on both sides. He was treated by *x*-irradiation to the upper cervical cord. He died two years later. At necropsy a glioblastoma was found extending from C 1 to C 5 segments of the cord and into the medulla in a spindle fashion lying in the central grey matter. The nuclei of the seventh, ninth, tenth, eleventh, and twelfth cranial nerves were intact, the upper end of the tumour being at least 2.5 cm. from the facial nerve.

In this case a lesion of the upper cervical segments of the cord, not involving the facial nerve intracranially but affecting those cord segments which give origin to the fibres of the great auricular nerve, has resulted in a lower-motor-neurone facial palsy.

It thus appears that irritation of the second and third cervical nerve roots (fibres of which form the great auricular nerve) by the herpetic virus or by fracture of the odontoid process of the axis, lesions of the upper cervical segments of the cord or nerve roots, or irritation of the great auricular nerve by trauma, *x*-irradiation, or alcohol may all give rise to a facial palsy of lower-motor-neurone type, although not directly involving the facial nerve. Interruption of the great auricular nerve may rapidly cure this.

"Rheumatic" Facial Palsy (Bell's Palsy)

In cases of typical "rheumatic" Bell's palsy there is not infrequently a history of exposure of the side of the neck to draught or dampness. Preceding the onset of palsy the patient often complains of pain, tingling, or neuralgia in the retroparotid region, over the side of the head and neck, in front of or behind the ear, in the auditory canal, and perhaps on the cheek or around the eye. The painful parts may later feel swollen, numb, stiff, gritty, or unreal and are often tender on pressure, and sometimes there is hyperalgesia in a small area around the ear (Wilson, 1940). The painful regions, it will be observed, are all supplied by the fibres of the great auricular nerve and are those to which pain radiates when the nerve is injected with alcohol. In almost all the cases of "rheumatic" Bell's palsy observed since this work was undertaken there has been acute tenderness on pressure over the course of the great auricular nerve as it lies on the sternomastoid muscle, and this will often cause pain to shoot up in front of and behind the ear or into the temporal region.

In 20 successive cases of Bell's palsy with pain and paraesthesiae as described above I infiltrated the great auricular nerve with 2% procaine. This resulted in immediate and complete relief of the pain and a disappearance of the swollen, numb, or tight feeling in the face and head. This lasted as long as the anaesthetic acted. Afterwards, however, pain and paraesthesiae were often greatly diminished or had almost ceased. This indicates that the sensory disturbances in cases of Bell's palsy must be the result of a disturbance of the great auricular nerve. As symptoms of the disturbance often precede the facial palsy by some days, the suggestion is that the primary lesion in such cases is a neuritis of this nerve set up in some cases by exposure of the side of the neck to cold or dampness.

Most observers are of the opinion that in cases of Bell's palsy the lesion of the facial nerve occurs originally near the exit of the nerve from the stylo-mastoid foramen, and that the oedema and inflammatory change may then spread upwards into the Fallopian canal. In favour of this is the fact that in early stages the sense of taste on the anterior two-thirds of the tongue is preserved, so that the lesion is presumably distal to the origin of the chorda tympani branch. Cawthorne (1951) found swelling and constriction of the nerve at the stylo-mastoid foramen in cases on which he operated. It therefore seems that, preceding the onset of a "rheumatic" Bell's palsy, there is usually evidence of a neuritis of the great auricular nerve, while the lesion of the facial nerve begins in the region where the great auricular nerve joins the facial nerve or in the territory of supply of the former.

Summary

Evidence is brought forward to show that in a large proportion of cases a lower-motor-neurone facial weakness constituting a Bell's palsy is the result of a neuritis or irritation of the great auricular nerve, which extends into the facial nerve as it lies in the region of the parotid gland.

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Northern Ireland, with its population of about 1,300,000 people, built 48,272 permanent houses in the period 1944–54. Including conversions, hutments, and temporary houses the total is 51,137. Of permanent houses local authorities built 18,893; the Northern Ireland Housing Trust, 12,376; housing associations, Government Departments, etc., 715; private persons with subsidy for letting, 2,590; owner occupiers, 9,883; industrial workers, 257; farmers and farm workers, 488; private persons with subsidy, 2,487; and rebuilt after war damage, 583.

PROLONGED LOCAL ANALGESIA WITH BENZOCAINE–URETHANE SOLUTION

BY

J. KOHN, Med.Dip.Lwow, D.C.P.Lond.
Senior Registrar, Department of Pathology

A. G. RUTTER, F.R.C.S.Ed.
Head of Department of General Surgery

AND

M. VITALI, Med.Dip.Warsaw
Registrar, Orthopaedic Department
Queen Mary's Hospital, Roehampton

During the last few years much interest has been centred on attempts to find a local analgesic drug or combination of drugs with an action prolonged over several days or weeks (McCleery *et al.*, 1948; Lewis and Thompson, 1953; Davidson, 1953). Such a preparation, if it were proved to be safe and free from undesirable side-effects, would have a wide field of usefulness. Most of the preparations so far advocated, however, including the recently introduced "efocaine" (Puderbach and Shaftel, 1952; Roualle, 1952; Oldham, 1953), have drawbacks and disadvantages which prevent their gaining widespread acceptance.

This paper briefly presents our experiences with a benzocaine–urethane solution, which in our hands has proved eminently satisfactory and free from undesirable side-effects. This solution was first described by Rappaport (1946) and by Spira (1946): its use in this country was referred to by Kohn and Vitali (1950) and by Rutter (1952).

Mechanism of Prolonged Action

The solution used is a simple, easily prepared one. It consists of a solution of benzocaine 2% and urethane 40% in distilled water. In these proportions the solution, though saturated, is stable: dilution with water or by contact with tissue fluids results in the precipitation of the benzocaine in micro-crystalline form. A "depot" is thus formed from which the active agent is slowly absorbed, resulting in a prolonged but strictly localized analgesic action. We have carried out experiments, both *in vitro* and *in vivo*, to confirm that this deposition in crystals does actually occur. Even a small amount of water added to the solution in a test-tube causes an immediate turbidity: by filtration of the precipitate and measurement of its melting-point, we were able to establish that it is indeed pure unchanged benzocaine. In the tissues the crystals may readily be demonstrated by direct examination of thick sections without embedding; their gradual fragmentation and disappearance may be followed by taking specimens (using legs destined for amputation) at increasing intervals of time.

Preparation and Properties

The solution is prepared as follows. To a 40% solution of urethane in distilled water, benzocaine (*para*-aminoethyl benzoate) is added in the proportion of 2%. The mixture is slowly warmed until the benzocaine is dissolved, and is allowed to stand for twenty-four hours. It is then filtered into screw-topped bottles of 20-ml. capacity and sterilized by autoclaving. We have shown that autoclaving does not result in a loss of more than 8–10% of the benzocaine, and that the *p*-amino-benzoic acid produced is quite non-toxic. Once sterilized the solution requires no preservatives and has active bacteriostatic properties against heavy inocula of all the common pathogenic organisms. The solution so prepared is a clear colourless one, with *p*H of 7.4 and a viscosity of only 1.93 (water equals 1). The low alkalinity and low viscosity are two of the most valuable properties of the solution in comparison with other preparations recently introduced.

Technique of Injection

The solution being a hypertonic and highly saturated one, and the method of action being that of the laying down of depots of a relatively insoluble active agent, certain precautions are essential in its use. From our own experience and that of others we have evolved the following rules, observance of which is essential if efficient action is to be achieved and undesirable side-effects are to be avoided.

(1) Syringes and needles must all be dry. Even a small amount of water is enough to cause some precipitation of the benzocaine; blocked needles and inaccurate dosage will arise if this precaution is not observed.

(2) Injections into the dermis must be carefully avoided, and superficial subcutaneous injections should be made only into normal healthy tissue. Injection into inflamed areas or into avascular scar tissue may cause necrosis. We have had one case, in our early experience, in which injection into a painful adherent scar resulted in an indolent ulcer which took several weeks to heal.

(3) The injection is essentially a "depot" one, and too large an injection into any one site may lead to the formation of painful nodules and to undue tissue reaction. This applies especially to injections near the skin surface. For most purposes a depot of 1 ml. is the largest which should be made at any one spot. The solution may well be used for the anaesthetization of wound edges by local injection: but instead of the ordinary continuous infiltration technique it must be placed in discontinuous depots of 0.5 to 1 ml., spaced at intervals of about 2 cm. Continuous analgesia will be secured by the overlapping of the small zones produced around each little depot.

(4) Nerve block is in general preferable to local injection, and it is in this field that the solution has its greatest usefulness. Direct injection into the nerve itself is to be avoided, and the aim should be to surround the nerve with a zone of small depots. While up to 2 ml. may be safely injected into the deeper tissues around the nerve trunks, it should be noted that, provided the depots are accurately placed, there is nothing to be gained by larger injections. Absorption is so slow and localized that increasing the size of the depot does not materially increase the area affected, and for almost all purposes individual injections of 1 ml. or less will give the best results. Two closely placed depots of 0.5 ml. each are probably preferable to a single one of 1 ml.

(5) The solution causes a temporary painful reaction, probably due to its hypertonicity. Injection should be done either under general anaesthesia or after preliminary injection of aqueous procaine.

Post-operative Pain Relief

The use of benzocaine–urethane solution for the relief of post-operative pain was first described by Winkler (1951). After experimenting with a number of different techniques we have now adopted a routine block of intercostal nerves 6 to 11, in the mid-axillary line, as the most effective method of achieving relief from the pain of upper abdominal operations. More posteriorly placed injections, which have been used by some workers, carry the risk of tracking of the solution through the intervertebral foramina into the spinal theca; more anteriorly placed ones will miss the lateral cutaneous branches and so fail to produce complete analgesia. A single injection of 1 ml. (or, better, two of 0.5 ml. each, 1 cm. or so apart, made through the same skin puncture) is introduced at the lower border of each rib. Provided care is taken with the accurate placement of the solution, such a regional (bilateral) block produces analgesia over the whole upper abdomen which has always persisted up to the time of removal of the stitches. No effect on the motor function of the nerves has been observed in over 60 cases treated. In those few patients who

have complained of pain in the wound, a careful examination has always revealed that one or more nerves has been missed owing to faulty technique.

We have treated 60 patients by this method after subtotal gastrectomy, and have been greatly impressed by their freedom from discomfort in the immediate post-operative days. To gain some objective measure of the efficiency of the pain relief achieved, we compared the number of injections of sedative (nearly always "omnopon") required by 20 consecutive patients, with that required by a consecutive 20 not injected with the benzocaine–urethane solution. The figures are given in Table I.

TABLE I.—*Number of Injections of Omnopon Required by 20 Non-injected and 20 Injected Patients in First Three Days After Gastrectomy*

	1st day and night	2nd day and night	3rd day and night	Total
Control series	41	35	14	90
Injected series	26	30	16	72

The most striking feature of the comparison is the reduction in the call for pain relief in the first day and night. It is even better demonstrated by an analysis of the individual patients, which shows that whereas none of the 20 non-injected patients got through the day of operation and the succeeding night without having at least two injections for relief of pain, only 4 of the 20 treated patients needed more than one. It is in the first twenty-four hours after operation that the likelihood of pulmonary collapse is greatest, and any reduction in the administration of morphine and similar drugs in this period must be to the patient's benefit. The difference in the succeeding days is less marked, perhaps because pain at this stage is related more to bowel distension than to the incision. One or two patients have complained of slight "stiffness" over the ribs for the first few days, but severe pain or paraesthesiae have been completely absent. A few have noted persistent numbness of the abdominal wall, but in none has it been a symptom of any seriousness or in any way interfered with normal convalescence.

Treatment of Amputation Neuroma

This is a notoriously difficult subject, and the assessment of the efficiency of any method of treatment is so bound up with psychological factors as to be almost impossible. We do not discuss in this paper the relative merits of the various methods of treatment, but merely seek to record the efficacy of the benzocaine–urethane solution in producing local analgesia and pain relief, and to lay down the rules for a satisfactory technique for the benefit of those who seek a long-acting anaesthetic for use in this condition.

One of us (M. V.) has now treated 60 patients by the local injection of benzocaine–urethane solution. A few were patients with painful scars of the extremities, but most of them were amputees. The cases fell into three classes: (1) painful stumps with tender palpable neuromata; (2) stumps with painful adherent scars; and (3) painful stumps associated with phantom pain. All patients had received previous treatment by a variety of methods, in most cases over a period of years. Previous non-operative methods of treatment included physiotherapy, percussion (Russell and Spalding, 1950), and the injection of aqueous local analgesics, while many of the long-standing cases had had repeated surgical treatment—excision of neuromata, excision of scar, and reamputation. A preliminary test injection with 2% procaine was performed in all cases; and no patient was treated with benzocaine–urethane unless substantial relief of pain lasting at least one hour could be secured by the test injection.

The injection itself was carried out under local analgesia in most cases, but a few apprehensive patients received general anaesthesia. Direct injection of the solution either subcutaneously or around a neuroma produces a temporary burning pain of considerable severity, so that some form of anaesthesia should always be used.

Injection is carried out according to the rules already laid down. Direct injection into the neuroma or nerve trunk is avoided, and the aim of the techniques is to surround the neuroma with a series of small depots placed closely enough to have a confluent action. A large neuroma may thus have as many as 12 or even 20 separate injections (made, of course, without more than one or two actual withdrawals of the needle). The smallest amount of solution used was 1 ml. and the largest 20 ml., and care was taken to avoid depositing more than 1 ml. in any one spot. The only complication seen was occasional mild local swelling and redness at the injection site, which always subsided without specific treatment in from one to three days. In no case did any necrosis, sloughing, or abscess formation develop.

Results

Of the 60 patients treated, 12 failed to gain relief beyond that so often seen after the injection of aqueous procaine. Of these, seven were classed as "predominantly functional" and four actually had, after psychiatric consultation, electric convulsion treatment, also without relief; in two others the pain was later shown to be due to an ill-fitting prosthesis, and was relieved when this was corrected. The remaining 48 all gained worth-while relief of pain. In a few, followed for from six to twenty-four months after the first injection, no further treatment has been necessary. The majority, however, after a period of one to three months, experienced a return of pain: a number of these were so favourably impressed by the result of the first injection that they returned asking for more, and no patient refused a second injection when it was advised. In every case the relief given by the second injection lasted longer than that from the first; and in those patients who again relapsed a third injection gave relief, which has so far been permanent. Detailed analysis and follow-up are not described in this paper, which is concerned primarily with the properties and uses of benzocaine–urethane, and not with a discussion of the treatment of painful stumps. The histories in 10 typical successful cases are summarized in Table II as an indication of the results which may be expected.

TABLE II.—*Histories of 10 Representative Cases of Painful Stump Treated with the Benzocaine–Urethane Solution*

Case	Age	Duration of Symptoms	Previous treatment	Amount Used	Duration of Relief
1	54	10 yrs.	Physiotherapy, percussion	4 ml.	1st injection, 2 months; 2nd, 4 months
2	61	12 yrs.	Physiotherapy, trim of stump	3 ,,	1st injection, 1 month; 2nd, 6 months
3	34	3 mths.	Physiotherapy	2 ,,	No recurrence after first injection
4	56	12 yrs.	Physiotherapy, percussion	8 ,,	1st injection, 1 month; 2nd, 3 months; 3rd, no recurrence
5	53	6 yrs.	Physiotherapy, percussion	5 ,,	1st injection, 2 months; 2nd, 3 months
6	65	8 yrs.	Physiotherapy, injection	3 ,,	1st injection, 1 month; 2nd, 2 months; 3rd, 6 months
7	29	10 yrs.	Physiotherapy	4 ,,	1st injection, 1 month; 2nd, 4 months
8	38	2 yrs.	,,	3 ,,	1st injection 3 months; 2nd, 6 months
9	27	4 yrs.	Excision of neuroma	2 ,,	No recurrence after first injection
10	35	10 yrs.	Physiotherapy	4 ,,	1st injection, 1 month; 2nd, 3 months; 3rd, 6 months

In all cases the duration of relief after the last injection continues, and no patient has so far required more than three injections.

Summary

A 2% solution of benzocaine in urethane has been used to produce prolonged local analgesia for the relief of pain after upper abdominal operations, and in the treatment of painful amputation stumps. Other workers have described its use in proctology (Spira, 1946; Rachet *et al.*, 1950), in gynaecology (Dresel, 1949; Arnous and Rey, 1951), and in the relief of pain of rib fractures (Winkler, 1951).

The solution has proved free from the drawbacks and disadvantages affecting all the preparations previously described. It has the great advantages of low viscosity (so that accurate injection is easy without the use of special syringes) and of an almost neutral reaction (and hence freedom from irritant effect and from the tendency to tissue necrosis). A third argument in its favour is that it is easily prepared and sterilized in any hospital dispensary; a quantity sufficient for a full intercostal block costs only a few pence.

This solution is advocated as the best at present available for further experimentation by surgeons interested in the possibilities of prolonged local analgesia.

We have to thank the Chief Medical Officer, Ministry of Health, for permission to publish this paper.

ADDENDUM.—Since this paper was written reports have appeared of the toxicity, especially on intravenous injection, of some of the proprietary preparations used for prolonged analgesia. As accidental intravenous injection is always a possibility in performing intercostal block, or in injecting a large nerve, we have had toxicity tests carried out on the benzocaine–urethane solution. Dr. A. C. White, of the Wellcome Research Laboratories, has kindly performed tests which show that in mice, while intravenous injection in a dosage of 2.5 ml. per kg. is uniformly fatal, a dose of 1.25 ml. per kg. can be given to a consecutive series of 10 mice without ill effect. Such a dose is, of course, about one hundred times as great as would be injected in any one site in our technique, and ten times the total dosage needed for a complete bilateral intercostal block. It would seem, therefore, that this is a hazard which need cause no serious concern to users of this solution.

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STELLATE GANGLION BLOCK IN GENERAL PRACTICE

BY

R. CROSBIE WALSH, M.R.C.S., L.R.C.P.

Anaesthetizing or blocking of the stellate ganglion was originally described 20 years ago, but I can find no evidence to suggest that it has ever been recommended or used as a procedure suitable for the general practitioner. It may be of interest to record that I have performed this operation under normal general practice conditions on 342 occasions on 139 patients.

There seems to be little doubt that the credit for the origination of this procedure must be given to Professor René Leriche. He and Fontaine in 1934 were the first to refer to it. In 1936 he and Fontaine produced a further paper. Neither of these papers was the subject of much comment at the time. In their first paper they published the result of 200 stellate ganglion injections which they had done in the previous nine years, and stated that stellate ganglion infiltration was not effective unless it was followed by Horner's syndrome and facial vasodilatation.

In 1938 Mackey and Scott described 19 cases of apoplexy which they treated by stellate ganglion block. Of these, nine cases showed improvement. They summarized their results by saying that these did not justify the adoption of anaesthesia of the stellate ganglion as a routine method of treatment in apoplexy, but that further study was necessary before the method was rejected as of negligible value. Nevertheless, as in several of their cases Horner's syndrome was not produced, this cannot be regarded as a fair sample.

Most of my cases are those of hemiplegia due to cerebral thromboses. The attitude of the medical profession towards these has become one of nihilism. This state has arisen for several reasons: (1) There has not been sufficient effort to separate the three major causes —(*a*) cerebral embolism, (*b*) cerebral thrombosis, (*c*) cerebral haemorrhage; (2) it has been thought that cerebral damage is inevitable; (3) some patients have recovered without specific treatment (Gilbert and de Takats, 1948).

A clinical classification of cerebral vascular accidents on an aetiological basis of haemorrhage, thrombosis, or embolism is essential, since a patient suffering from cerebral haemorrhage should not be subjected to stellate block, or at least it should not be done until a long period of observation has indicated that bleeding has ceased (Butt and Mathers, 1948).

From my point of view the most significant symptom in the differential diagnosis between cerebral thrombosis and cerebral haemorrhage is the presence of neck rigidity in cerebral haemorrhage. If neck rigidity is present stellate ganglion block should be avoided. Any theory directed towards relief of a disordered physiological state brought about by cerebral thrombosis can have but one purpose, and that is to restore the blood supply to the specific area of the brain (Volpitto and Risteen, 1943).

Villaret and Cachera (1939) produced cerebral emboli artificially in dogs and watched the vessels of the pia through windows in the skull. These vessels went into spasm even in areas not directly affected by the emboli and persisted thus for some weeks. The sympathetic nerve supply to the cerebral vessels comes from the upper thoracic segments of the spinal cord and passes by way of the stellate and cervical ganglia. If, therefore, these are anaesthetized the cerebral blood flow is increased. Volpitto and Risteen (1943) made two trephine holes into the skull under local analgesia, and the cortex was visualized before and after injection of the stellate ganglion with procaine. They observed that the increase in the calibre of the pial vessels is limited to the affected side. The effect is immediate and does not increase with further time or additional procaine. The scalp and dural vessels become dilated, as do the vessels of the cerebral cortex.

If improvement is to follow a cervical sympathetic block the improvement should be noticed within ten minutes. Should there be a relapse, a further injection should be given (Gilbert and de Takats, 1948).

I have chosen for treatment cases of hemiplegia due to cerebral thrombosis, Raynaud's disease, severe cardiac pain in angina pectoris, and stiff shoulders. I have reported only cases in which there was an actual block of the stellate ganglion, this being shown by the presence of

Horner's syndrome, the components of which appear in this order: (1) narrowing of the palpebral fissure, (2) contraction of the pupils, (3) enophthalmos, and (4) absence of sweating on the side of the injection. To this must be added a noticeable increase of warmth on the injected side. Also, in half to three-quarters of the cases a conjunctivitis appears on the affected side.

Technique

In my series of cases an anterior approach to the stellate ganglion was used. This approach differs from that used by most other authors. It is done with a No. 1 serum needle on a 10-ml. syringe. The needle is passed medial to the sternal head of the sternomastoid muscle a finger-breadth above and lateral to the sternal notch. With the middle and ring fingers of the left hand the carotid artery is palpated and then moved laterally. The serum needle is inserted at a right angle and is pushed straight through just lateral to the trachea. In most cases there is no difficulty in hitting the transverse process of the seventh cervical vertebra. The stellate ganglion is situated between the transverse process of the seventh cervical vertebra and the neck of the first rib. Then 10 ml. of 1% procaine hydrochloride is injected. In my later cases, when there has been cerebral thrombosis I have injected bilaterally. With this method, as opposed to the more usual anterior approach through the two heads of the sternomastoid, most of the complications are avoided. These are: puncture of the subclavian artery, puncture of the meninges, and surgical emphysema or pneumothorax (Leriche and Fontaine, 1934).

The Table shows the results of 124 cases of cerebral thrombosis treated in this way. It is apparent that improvement was present in 17 out of the 23 cases seen within 24 hours. The interesting feature at the other end of the scale is that of the long-standing hemiplegias. Within 6 to 12 months there was some improvement in 4 out of 22 cases. Leriche (1952) gives one injection of 10 ml. a day for 15 days for the "strokes" of recent origin, and in the longer-standing cases he gives 12 to 36 injections. It has not been possible for me to give as many as this, but if some degree of recovery has not taken place within three injections I count it as a failure.

Results

Time Lapse	No.	Complete Recovery	Good	Fair	No Improvement
Within 24 hours ..	23	12	5	0	6
„ 2–7 days ..	27	8	6	9	4
„ 1–4 weeks ..	18	1	5	5	7
„ 1–6 months	34	0	0	8	26
„ 6–12 „ ..	22	0	0	4	18
Total ..	124	21	16	26	61

Raynaud's Disease.—Three cases were treated: one had relief for one week, and one for one month, in the third there was no effect. This is a very small number of cases, but it was interesting to see that the effects on the second arm were identical with those on the first.

Cardiac Pain in Angina Pectoris.—In general practice one is confronted always with a few cases of long-standing angina pectoris. Some of these patients may have had a coronary thrombosis 10 to 15 years ago, and in others the electrocardiogram is normal or almost so. I have been very careful to select cases of long standing for injection. Of the five cases treated, two had complete relief, two had some relief, and in one there was no effect. In all these cases bilateral ganglion blocks were done.

Stiff Shoulder.—In all cases these were post-traumatic. There is a time in treating this type of shoulder when active exercises and heat are producing very little result and the interval is too short since the time of injury for manipulation under an anaesthetic. This small series of seven cases represents those patients seen in general practice during the course of the last year: two had complete relief, one had slight improvement, and in four there was no effect.

Summary

The stellate ganglion has been injected 342 times in 139 patients. These patients were seen in a general practice in South London and the injections took place in the patient's own home, the consulting-room, nursing-homes, an L.C.C. welfare home, and the out-patient department of a general-practitioner hospital. A technique of the anterior approach to the stellate ganglion is described, and it is suggested that this is a safe procedure for use in general practice. The general practitioner obviously sees more cases of cerebral thrombosis first, and it is comparatively easy for him to inject the stellate ganglion within the first 24 hours. With this short time lag the prospect of a complete recovery or great improvement is very great. In this series of cases the procedure itself has not given me a moment's anxiety.

I should like to thank my colleagues for allowing me to anaesthetize the stellate ganglion in many of their patients.

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GYNAECOMASTIA IN TWO BROTHERS

BY

D. G. FERRIMAN, D.M., M.R.C.P.

Physician, North Middlesex Hospital

In 1950 I reported on a youth of 17 suffering from gynaecomastia. Subsequently the same condition developed in the younger brother. The latter has been investigated, and further studies have been carried out on the elder brother.

Case 1

The elder brother was first seen in 1947, aged 17. He complained of breast enlargement, which started at the age of 14. He had never shaved and had had neither erections nor emissions. Libido seemed to be absent. His hobbies were those of a boy. He had suffered no injuries to or disease of the testicles.

Pronounced gynaecomastia was present (see Fig. 1). The penis was small and the urethra opened at the base of the glans. Scrotum and testicles appeared normal. The pubic hair was of feminine distribution and axillary hair was scanty. The face was covered with a fine down. His height was 63½ in. (161 cm.) and span 66 in. (168 cm.); head to pubis measured 32 in. (81 cm.) and pubis to ground 31½ in. (80 cm.). His voice was soft and his manner retiring. There was no plethora or glycosuria, and the blood pressure was normal.

His bone age corresponded to chronological age. 17-ketosteroid excretion was considered to be within normal limits. Although the original estimate was rather high, this was not confirmed by subsequent tests, which yielded figures of 12, 18, and 14.5 mg. within 24 hours. The original estimate of F.S.H. excretion was regarded as being within normal limits (Dr. A. M. Hain). Another, some months after a period of testosterone therapy, showed a 24-hour output of more than 40 and less than 160 units

FIG. 1.—Case 1.

FIG. 2.—Case 2.

(Dr. G. I. M. Swyer). A further estimate six months later revealed less than 10 units per 24 hours (Dr. G. I. M. Swyer).

A breast biopsy by Mr. Page showed hyperplasia of duct elements and fibrous tissue (Dr. J. F. Heggie). Laparotomy revealed neither uterus nor Fallopian tubes, and the adrenals appeared normal on palpation. Testicular biopsy and mastectomy were refused.

Case 2

The younger brother was first seen in 1950 at the age of 18. He complained of breast enlargement, starting at the age of 17. He had never shaved nor had emissions, but he had experienced erections for one year. His hobbies were those of a boy. He had suffered no injury to or disease of the testicles.

Physically he closely resembled his brother (see Fig. 2). Breasts, penis, testicles, hair distribution, voice, manner, and general appearance were almost identical. His height was 60 in. (152 cm.) and span 63½ in. (161 cm.); head to pubis measured 29 in. (74 cm.) and pubis to ground 31 in. (79 cm.). Two 24-hour estimates of 17-ketosteroid excretions were 8.9 and 17.5 mg. (Dr. A. B. Anderson). Two estimates of F.S.H. excretions were performed: one revealed less than 5 units in 24 hours, and the other between 5 and 10 units in 24 hours (Dr. G. I. M. Swyer).

Further investigations, including testicular biopsy and mastectomy, were refused.

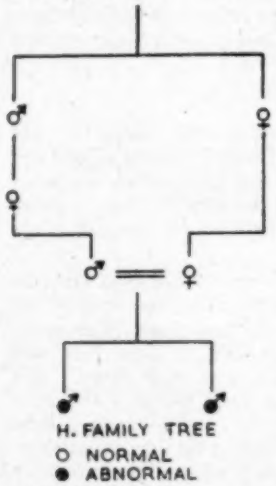

FIG. 3.—Family tree.

Family History

The father and mother are related, as shown in Fig. 3. The father had one brother and four sisters, and the mother four brothers and six sisters. No abnormality resembling the present condition was known of in the family, nor was there any history of primary amenorrhoea in the females; all but one of the nine married aunts and uncles have had children.

Case 1 at the age of 22 and Case 2 at the age of 20 were both 161 cm. in height. So far as was known, the female members of the family on both sides were of the same size or taller, and the men with one exception distinctly taller. The two brothers therefore seem to be unusually small.

Discussion

The condition is clearly hereditary in nature. The consanguinity of the parents and the apparent absence of similar abnormality in other members of the family suggest a recessive mode of inheritance.

In the absence of a biopsy, the precise gonadal lesion and the diagnosis must remain in doubt. Ovotestes may have been present, when the diagnoses of hermaphroditism would apply; the failure to find a uterus or Fallopian tubes at laparotomy in the eldest brother is somewhat against this explanation. Testicular hypoplasia is a possibility. The low figures for F.S.H. excretion may indicate a pituitary origin for such hypoplasia, and the tendency to dwarfism—consistent with a deficiency of growth hormones—may therefore be significant. The one high figure for F.S.H. excretion in the elder brother followed a period of testosterone therapy, and may well be a rebound phenomenon. Alternatively, the testicular cells responsible for secretion of the substance inhibiting gonadotrophin production may have been spared in a primarily gonadal hypoplasia.

The mechanism for the development of gynaecomastia in testicular hypoplasia is obscure. Oestrogen excretion has been investigated in a number of cases and found within normal limits (Klinefelter *et al.*, 1942; Heller and Nelson, 1945). Excess of circulating gonadotrophin is clearly not the explanation in these two patients.

Summary

Gynaecomastia has been found in two brothers. Testicular biopsies have not been obtained, and aetiology is uncertain. Ovotestes with hermaphroditism and testicular hypoplasia are possibilities. The condition appears to have been inherited in a recessive manner.

I would like to thank Dr. G. I. M. Swyer for the gonadotrophin assays in these patients, and Mr. C. W. Hall for the photographs.

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Medical Memoranda

A Case of Inversion of the Uterus

Inversion of the uterus is such a rare condition that the following case of inversion of the non-puerperal uterus caused by a fibroid is worth reporting.

The incidence of puerperal inversion is about 1 in 30,000 labours (Das, 1940) and the non-puerperal condition is even more uncommon. Das, in a study of 391 cases of inversion, found that 16.35% were non-puerperal, and McCullagh (1925), in an analysis of 233 cases recorded in the literature between 1911 and 1924, found 15%.

CASE HISTORY

A 0-gravida, aged 35, was admitted to hospital on December 15, 1951, complaining of severe vaginal bleeding for the past seven days. Since the age of 15 her periods had been regular, lasting five days and recurring in a 28-day cycle. The loss was not heavy except on rare occasions, and there was no dysmenorrhoea. Seven days before admission a period had started on the expected date. The loss was very heavy from the beginning and the patient was confined to bed. There were no other symptoms except slight lower abdominal discomfort. She had no pain or nausea, no difficulty on micturition, and no bowel symptoms. On the seventh day her face and hands became numb. Her doctor arranged for her immediate transference to hospital.

On admission she was found to be extremely exsanguinated. Her temperature was 97.8° F. (36.6° C.), pulse rate 116, and blood pressure 115/65. Haemoglobin

was 22%. There was no abdominal tenderness or guarding. Vaginal examination revealed a swelling, about 5 in. (12.5 cm.) in diameter, arising from the vault and filling the cavity of the vagina. She was bleeding freely.

She was examined under general anaesthesia after transfusion. The fundus of the uterus was not palpable on bimanual examination and there was no cervical rim. The swelling in the vagina was irregular and had the consistence of a fibroid. The diagnosis of complete inversion of the uterus associated with a submucous fibroid was made. It was difficult to distinguish between the uterus and the tumour, and, for this reason and because of the poor condition of the patient, it was decided to attempt to replace the uterus instrumentally. A biopsy confirmed that the tumour was a fibroid. An Aveling repositor was inserted and the vagina packed with acriflavine and glycerined gauze.

During the next three days the repositor and pack were removed daily, but on each occasion there was severe haemorrhage. The uterus remained inverted. On the third day the repositor was abandoned, but the vagina was repacked daily in an attempt to control the bleeding. In all, 15 pints (8.5 litres) of blood was given by transfusion during these days. On the fourth day the temperature rose to 99.6° F. (37.6° C.) and a high vaginal swab was taken; this subsequently grew *Bacterium coli* and haemolytic streptococci. During the next 10 days 11,500,000 units of penicillin and 18 g. of streptomycin were given.

On the sixth day her general condition had improved and she was again examined under general anaesthesia. A Schuchardt incision was made. The fibroid was gripped with a vulsellum, and by using considerable force the uterus and the fibroid were delivered out of the vagina. The uterus was elongated and completely inverted, and there was no cervical rim. The fibroid was 4 in. (10 cm.) in diameter, was submucous and sessile, and was attached to the fundus of the uterus. There was still profuse bleeding from the endometrium. The capsule of the fibroid was incised all round about 1 in. (2.5 cm.) from the uterine wall and the fibroid was enucleated from its bed. The uterus was replaced digitally without difficulty by pressing on the centre of the fundus. As soon as the uterus was in its normal position haemorrhage ceased.

Convalescence was uneventful. There was a blood-stained vaginal discharge for three days and thereafter no loss at all. The patient did not complain of pain or discomfort. Her temperature rose to 101° F. (38.3° C.) on the two evenings following operation and then remained normal. She was discharged 17 days after operation, the haemoglobin then being 78%. The uterus was slightly enlarged, anteverted, and not tender. The cervix was patulous, and the external os could admit two fingers. There was no vaginal discharge.

Pathological examination of the fibroid showed it to be 4½ by 3 in. (11.4 by 10 cm.) in diameter, with the typical whorled appearance on cross-section.

COMMENT

The cause of inversion in this case was undoubtedly the uterine fibroid. There were no symptoms except haemorrhage and it was not possible to determine when inversion had occurred. The patient firmly denied having had any pain.

In considering treatment, her age and general condition at the time of both operations were taken into account. Infection was slight and did not complicate the issue. Vaginal hysterectomy would have been practicable, but as she was only 35 conservation of the uterus was thought to be desirable. Replacement with Aveling's repositor was attempted before it was appreciated that the fibroid was larger than the uterus. Myomectomy presented no difficulty once the fibroid had been defined, and manual replacement was then easy.

I wish to thank Mr. John Beattie and Mr. Kenneth Watson for permission to publish this case.

MARY R. ELLIS, M.B., B.S., M.R.C.O.G.,
Obstetric Registrar, North Middlesex Hospital.

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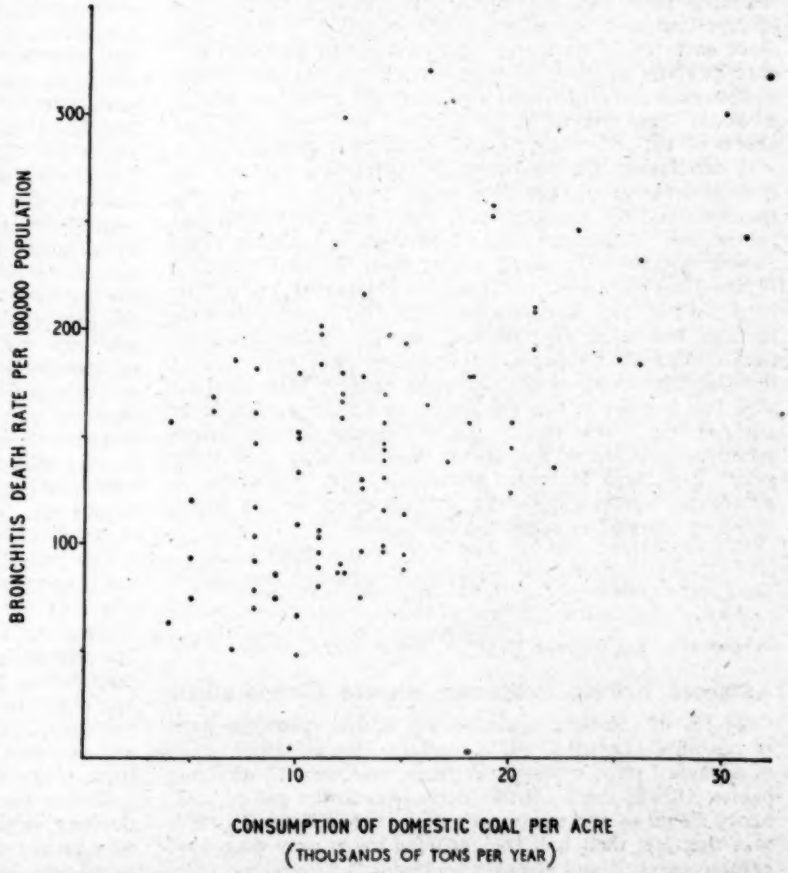
Air Pollution and Bronchitis

The results recorded in the interesting paper by Pemberton and Goldberg (1954) agree with the results of a similar analysis carried out by the Social Medicine Research Unit of the Medical Research Council. This analysis covered the five years 1946–50, but, unfortunately, only 15 county boroughs were equipped with lead peroxide instruments for the measurement of sulphur dioxide pollution throughout that period, and only 24 county boroughs gave an alternative measure of sulphur pollution (SO_4'', as a dissolved impurity in deposit gauges). Nothwithstanding this, the correlation coefficients we obtained were very similar to those given by Pemberton and Goldberg, at least so far as males aged 45–64 years were concerned. ($r=0.51$, using the first index of pollution; $r=0.32$, using the second. Average figures for the five years were studied.) Like the two authors, we felt that the pollution records were unsatisfactory—particularly in view of the considerable variation between stations in the same county borough.

Because of this, and because of the very few towns involved, we tried to find some better and more universal measure of the amount of atmospheric pollution to which the inhabitants of towns and cities were subjected. It was



Relationship between the consumption of domestic coal per acre in 1952 and the average annual death rates from bronchitis of males aged 45–64 years for the three years 1950–2, in the 83 county boroughs of England and Wales. Correlation coefficient = 0.59 ($P<10^{-6}$).

eventually decided that some index based on the amount of coal consumed annually by each town would be worth investigating, and the Ministry of Fuel and Power has recently been kind enough to give us access to such figures. So far, only some very preliminary analyses have been done, but interesting results are beginning to emerge. The Chart, for example, confirms some of the findings of Pemberton and Goldberg and extends them to all 83 county boroughs. This diagram shows the relationship between average annual mortality from bronchitis in males aged 45–64 years in the three years 1950–2, and the consumption of domestic coal per acre in 1952, in the county boroughs of England and Wales. The coefficient of correlation between these two indices is 0.59, which is highly significant (probability less than one in a million). To ensure that this high correlation was not merely the reflection of a relationship between the two variables and a third—namely, the poverty of the towns—the proportions of occupied and retired males in social classes IV and V in the various county boroughs were taken into account, but this only reduced the correlation coefficient to 0.52. Similarly, allowing for differences in the amount of overcrowding (measured by the proportion of persons living more than one per room) only reduced the correlation coefficient to 0.53. Both of these figures are still highly significant.

These results are surprising for two reasons. (1) The measurement of acreage refers to the total area of the county borough, and has been taken from the 1951 census volumes. It only bears a rough relationship to the actual area lived in, since much agricultural land is often included inside the borough boundaries. We hope to be able to obtain a rather more accurate measure of the relevant areas at a later date. (2) Only the consumption of domestic coal has been considered, although this amounts to a mere 18% of the consumption of all coal, on the average. It is worthy of note that the coefficient of correlation between these bronchitis mortality rates and the annual consumption of *all* coal (except that used by railways and shipping) is only 0.24. Since each ton of coal used for non-domestic purposes discharges about as much sulphur dioxide into the atmosphere as does each ton of domestic coal, but very much less smoke, it would seem premature to attribute the apparently bad effects of air pollution primarily to sulphur dioxide.

In conclusion, the coefficient of correlation between the index of atmospheric pollution based on domestic coal consumption and the average death rate from "bronchitis and pneumonia" of females aged 45–64 years in the three years 1950–2 is 0.54—very much higher than the corresponding figures (for bronchitis) obtained by Pemberton and Goldberg. We do not feel, however, that this contradicts their findings, but rather that the low (though consistently positive) coefficients which they found may have been due to the fact that in some of the towns used in their analysis very few females in this age group died from bronchitis in any one year. This would tend to diminish the correlation coefficient. It is for this reason that we have used three years' data, and included pneumonia with bronchitis (a procedure, incidentally, which has no effect on the corresponding correlation coefficient for males).

C. DALY, B.Sc.,
Statistician, Social Medicine Research Unit, Medical Research Council.

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Advanced Ectopic Pregnancy without Complications

Only 1% of ectopic pregnancies are said to reach the stage of viability (Dorman, 1951), and in 260 published cases of advanced ectopic pregnancy there were only 12 surviving babies (Ulrich, 1946). If the foetus lives to the end of pregnancy diagnosis and treatment may be very difficult (Dorman says that less than half the recorded cases were diagnosed before operation and gives the maternal and foetal mortality rates as 15% and 76% respectively). There is a high incidence of congenital defects (figures vary from 10% to 46%), and of babies born alive only half survive for more than a week (Dorman).

The case here recorded ran an uncomplicated course. There was no anxiety during pregnancy; positive diagnosis was made before operation; delivery was simpler than an ordinary caesarean section; there were no major complications after operation, and mother and child left hospital in good health.

CASE REPORT

A Punjabi woman aged 20 had had no antenatal supervision and came to hospital at approximately nine months because she thought that normal labour had begun. She had had two normal confinements, one and a half and two and a half years previously. There was no history of abortions or of venereal disease. She had noticed that foetal movements were less than during her previous pregnancies. There was slight leucorrhoea, and oedema of the left leg had been present for a month. Otherwise pregnancy had been normal.

Five days before delivery she had pain in the left loin and left iliac fossa following a fall. For two days she had quite severe intermittent colicky pain, which resembled labour pain. She was admitted to hospital on October 10, 1952, apparently in labour. A breach presentation of a fully developed foetus was confirmed by *x*-ray examination, and an unsuccessful attempt was made at external version. Pains continued but no progress was made. The foetal head was easily felt to the left of and slightly above the umbilicus. No foetal limbs were felt. A normal foetal heart was heard in the left iliac fossa. The os admitted one finger, and the cervical canal, which was long, led this finger forwards. No membranes or foetal parts were felt through the os, but a foetal foot was felt with surprising clearness through the posterior fornix. This led to a diagnosis of extrauterine pregnancy with the amniotic sac lying behind the uterus.

At operation, the uterus, about the size of a two months' pregnancy, was flattened against the anterior abdominal wall with the amniotic sac, covered by smooth peritoneum, presenting above and to the left of it. The right broad ligament was distended over what was obviously the placenta, the right Fallopian tube and round ligament being stretched across it. The ovaries and left tube appeared normal. There were no adhesions between bowel or omentum and amniotic sac or placenta. The placenta was covered by peritoneum in front, above, and behind, and was attached by a broad base deep in the pelvis. The amniotic sac covered by peritoneum was thin and transparent, and, though the liquor was meconium-stained, the head and hands of the foetus were clearly seen through it. The entire gestation sac was clearly extraperitoneal, no erosion of the peritoneum by the chorion having occurred anywhere. The sac was incised close to the foetal head and the foetus removed without haemorrhage. Removal of the placenta would certainly have necessitated hysterectomy, and, as it seemed that its circulation was connected with the great vessels of the pelvis, its removal would have been extremely hazardous. All foetal membranes and placenta were left *in situ*.

The baby (4 lb. 6 oz. (1.9 kg.), female) was cyanosed at first, but soon cried vigorously and appeared normal in every way and not premature. The mother was given "distaquaine," 300,000 units daily for six days, and also mepacrine, 300 mg. daily for 10 days. There was fever on two days only during the first week, almost certainly due to malaria. She chose to feed the baby artificially. It lost weight for four days, but had regained its birth weight by two weeks and was then vigorous and feeding well and apparently free from congenital defects.

During the puerperium there was a slight mucoid vaginal discharge which was sometimes stained with blood, but there were no normal lochia. Two weeks after delivery the abdominal scar was well healed. The uterus was felt displaced to the left, and the placenta, smaller than at operation, to the right of and behind the uterus, but its edges were not

easy to define. Six months later she was in excellent health. The mass in the lower right abdomen was still present but much smaller, and two normal menstrual periods had occurred.

COMMENT

The essential anatomy of this case was, in Schumann's (1931) classification, that of an extraperitoneal intraligamentary ectopic pregnancy. An uncommon type, it arises by slow erosion of the Fallopian tube so that the extruded ovum grows out between the layers of the broad ligament. At the time of operation the foetal circulation was still intact, and all tissues, foetal and maternal, were healthy. There was no haemorrhage, thrombosis, sepsis, or adhesions to complicate operation. The placenta, with its maternal blood supply intact, could be safely left and expected to undergo complete absorption.

Acknowledgments for permission to publish this case are made to the Director of Medical Services, Tanganyika.

H. T. LAYCOCK, M.B., B.Chir., F.R.C.S.,
Surgical Specialist,
Colonial Medical Service, Tanganyika.

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Transepiploic Hernia: Spontaneous Hernia through the Greater Omentum

Herniation of a viscus through a defect in the greater omentum is not common. The defect may arise *de novo*; it may follow surgery or disease. Dolton (1944), referring to mesenteric defects, quotes Prutz's classification, which can be applied to omental defects, as follows: (1) congenital, (2) spontaneous (arising as a primary condition during life), (3) following trauma, (4) following surgery, and (5) following inflammation. It is generally believed that most of these defects are acquired and belong to group 2. However, examples have been found in the full-term foetus; furthermore, it has been shown that if during development epithelial layers are opposed without enough intervening tissue they tend to fuse and leave a gap. Martzloff (1930) ascribes them simply to atrophy of connective tissue. Tanner (1946) notes that similar herniae through the transverse mesocolon occur in areas where the tissues are thin and tenuous and the blood supply poor. Reports of such spontaneous herniae are few. Johnson (1950), in a paper on internal herniae, mentions the conditions briefly. The most complete account appears to have been given by Gubler and Yedinak (1950). They quote Martzloff (1930), who found 15 reported cases that were recognized on account of the complication of obstruction or strangulation; all but one of these involved the small bowel, and no age group was exempt. Of nine who were operated on, eight recovered; in three unoperated cases the patients died; and the notes of the other three were incomplete. The authors quote five more cases since 1930 and report one of their own.

CASE REPORTS

The following two new cases occurred within one week of each other.

Case 1.—A boy aged 15 was admitted complaining of colicky central abdominal pain and vomiting for eight hours. He had eaten a number of green sour apples earlier that day. There was nothing relevant in the past or family history. His temperature was subnormal, pulse 100, respirations 20. His abdomen was a little distended, with generalized tenderness and guarding, most pronounced in the right iliac fossa, where there was a positive release sign. Bowel sounds were increased and obstructive in character; rectal examination was normal. Gastric aspiration and intravenous replacement therapy were started after a diagnosis of obstruction, with early strangulation, had been made. Through a right paramedian incision a moderate amount of free sero-sanguineous fluid was found. Distended coils of small intestine presented, and the site of obstruction was seen to be about 4 in. (10 cm.) from the ileo-caecal valve, where about 2 in. (5 cm.) of ileum had strangulated through a hole in the omentum close to its free border. The gut was viable, and it was easy to relieve the strangulation and prevent recurrence. Recovery was uneventful.

Case 2.—A woman aged 50 was admitted complaining of abdominal pain for 12 hours, which had at first been generalized but had largely settled in the right iliac fossa some four hours before admission. She had vomited twice and the bowels had not been opened since the onset. There was nothing relevant in her past or family history. Her temperature was 98.6° F. (37° C.), pulse 96, respirations 20. The tongue was slightly furred. Her abdomen was not distended, and, though there was some generalized tenderness, it was maximal with guarding and a positive release sign in the right iliac fossa. Per rectum there was tenderness on both sides of the pouch of Douglas. So far the history and physical signs suggested acute appendicitis, but on auscultation bowel sounds were increased. Through a right paramedian incision free fluid was found as in the first case. About 12 in. (30 cm.) of mid-small-bowel had strangulated through a hole in the omentum. The strangulation was more severe this time, but the gut was quite viable and relief was effected as before. Recovery was uneventful.

COMMENT

The behaviour of internal herniae differs from that of external herniae in one important respect. Whereas there is a pressure gradient in the latter between the general peritoneal cavity and the hernial sac keeping the contents in place, there is no such force in the case of the internal variety, unless superadded obstruction is present. Once obstruction has developed, the enhanced peristalsis of the proximal loop is unremitting and leads to strangulation. Partial obstruction (excluding Richter's type) and spontaneous relief do not occur in this form of hernia.

It follows that simple internal hernia, unlike the external, is a very transient and symptomless, though recurrent, affair, resulting from the normal movements of the bowel. It is only when the neck and sac are huge that the exception occurs. For practical purposes the contents of an internal sac remain in place only in the presence of obstruction, and it is thus only that the condition is recognized clinically. It does not feature as a cause of recurrent abdominal pain of the type associated wtih intermittent obstructive attacks.

At first sight it may seem unlikely that omentum, being unfixed, easily displaced, and in these two cases so flimsy, should form the neck of a hernia at all. At all other hernial sites the neck is fixed and its edges are relatively rigid. A very forceful peristalsis must occur to cause the bowel to pass suddenly through this yielding gap. This can be assumed to have happened in Case 1, the young boy first having had colic as a result of eating sour apples. Once the herniation has occurred the omental neck is likely to give way and tear to a certain extent. Soon, however, the effect of trauma, causing inflammatory congestion, turns the neck into an unyielding ring so that strangulation can occur.

In both cases mentioned the gap was close to the free edge of the omentum. The omentum was thin and lace-like, though no other holes were found.

I am indebted to Mr. T. W. Mimpriss and Mr. Murray T. Pheils, under whose care respectively these cases were treated, for permission to report them and for critical help in their presentation.

W. H. DAVIES, M.B., F.R.C.S.,
Late Surgical Registrar,
St. Peter's Hospital, Chertsey.

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Reviews

A.C.T.H. AND CORTISONE

The Effect of ACTH and Cortisone upon Infection and Resistance. Edited by Gregory Shwartzman, M.D. Symposium held at the New York Academy of Medicine, March, 1952. (Pp. 204+x; illustrated. 45s.) Columbia: University Press. London: Geoffrey Cumberlege. 1953.

Allow me to say at once what a neat little book this is and how much I enjoyed it. Its 204 pages, many of them given up to references, excellent illustrations, and tables, are packed with the most interesting, if at times puzzling and contradictory, facts described with admirable lucidity. If the reader emerges with a feeling of bewilderment it is not the fault of the contributors to this symposium. It is perfectly clear that we have at last come to grips with a puzzling problem, and the first flush of enthusiasm has given place to a more sober outlook. But let me outline very briefly what each contributor has to say in this discussion.

After a thoughtful introduction by Gregory Shwartzman, Engel leads us through the maze of intermediary metabolism, showing us where cortisone and A.C.T.H. intervene and reminding us that the adrenal is only one of a set of glands concerned with homoeostasis. Umbreit summarizes his interesting work on enzyme reactions in the rat, and with proper caution discloses that the enzymatic composition of the tissues may be altered by adrenocortical hormones, though he is not sure of the significance of these changes. Ehrich and Seifter develop the theme that corticosteroids have a depressing effect upon lymphoid tissue. Since these steroids are ineffective in washed-cell suspensions—the recent work of Trowell is not altogether in agreement with this statement, however—they suggest that such hormones require co-factors for their action. Ragan and his co-workers carry us a little farther in the search for the explanation of the depression of repair in connective tissue caused by cortisone, and seem to be coming round to the view that substances with chemotactic or stimulating effects on macrophages, fibroblasts, and new blood vessels must be seriously looked into.

Fischel gives an excellent survey of cortisone and allergy in which he says bluntly that experimental allergic reactions are not altered by these hormones. A clinical counterblast comes from Harvey, Shulman, and Schoenrich, who are moderate enough in their attitude. Stoerk gives instances of the depression by cortisone of inherited and acquired resistance to infection and to tumour grafting, a topic quite obviously in its immature stages; while Max Lurie and his colleagues summarize their neat quantitative investigations whereby they establish the action of cortisone on some mechanisms involved in the pathogenesis of tuberculosis. Turner and Hollander's chapter on cortisone and experimental syphilis is a model for experimentalists and again brings out the importance of host factors.

A group of workers under E. A. Kabat describe how cortisone can stir up latent trypanosomes in monkeys; and Kass *et al.*, after a pithy account of adrenocortical hormones in pneumococcal and influenza virus infections and in malaria, warn us that the clinical use of these hormones in infectious diseases must still be undertaken with caution. Lewis Thomas's work on the effects of cortisone on bacterial infection and intoxication has already been the subject of a first-rate editorial in the *British Medical Journal* (1954, 1, 381).

A stimulating account of their recent experiments on poliomyelitis in the hamster by Schwartzman and Aronson, which again stresses the importance of host factors, brings to an end a most successful enterprise. May the reviewer whisper that an index would have been useful?

G. R. CAMERON.

X-RAY AND RADIUM PHYSICS

The Fundamentals of X-ray and Radium Physics. By Joseph Selman, M.D. (Pp. 340+xii; illustrated. 61s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1954.

This volume aims at supplying the student *x*-ray technician with all the information he will require for the accurate performance of his work. Everything is explained in the simplest manner possible, and even the most elementary knowledge of arithmetic and mechanics is not assumed. By means of admirable diagrams and illustrations the student is taught the general principles of electricity and magnetism and their application in the construction of generators, motors, and current meters. The construction of *x*-ray tubes and of valves is clearly demonstrated and their use is well explained.

On the practical side full details are given of photographic methods, exposure and development, and the handling of films and the use of intensifying screens. Precise instructions are included on the application of these methods to *x*-ray practice and the problems of distortion, and on the use of grids and the Potter-Bucky diaphragm. In fact, every detail of the most modern practice is fully explained.

The book is indeed remarkable for the amount of technical information which it contains, the simplicity of its language, and the ingenuity and clearness of its illustrations. The student could have no better guide throughout his apprenticeship, but many others also will welcome this clear account of a fascinating field.

HENRY SOUTTAR.

RESPONSE TO EMOTION

Bodily Physiology in Mental and Emotional Disorders. By Mark D. Altschule, M.D. (Pp. 228. $5.75.) New York: Grune and Stratton, Inc. 1953.

This is a valuable source book for the worker interested in the physiological changes which may accompany emotional changes, both normal and pathological. The field covered is so vast, and the number of papers listed so great, that the task of evaluating the various contributions in any critical or integrative manner would be a Herculean one. Dr. Altschule has not attempted such a task, but he has tried to make, and to a large extent has succeeded in making, his review comprehensive. This is a useful achievement. The bibliographic value of the book would, however, be increased if the references were collected together rather than being printed after every chapter, and if the American custom of printing the titles of the papers had been adopted.

ALICK ELITHORN.

CEREBRAL PHYSIOLOGY

Physiologie des Lobes Frontaux et du Cervelet: Étude Expérimentale et Clinique. By John F. Fulton. Preface by Professor Alafouanine. (Pp. 158; 48 figures. 1,000 fr.) Paris: Masson et Cie. 1953.

Professor Fulton's published lectures on functional localization in the frontal lobes and cerebellum and on frontal lobotomy and affective behaviour are well known in this country. They have now been brought up to date and somewhat modified and published in French together with a terminal chapter on the work of the late Sir Charles Sherrington. It is interesting to note that some earlier views on functional localization in the frontal lobes and the so-called cerveau viscéral (expressed rather blatantly in a curiously phrenological diagram in Fig. 24) are becoming rather rapidly dissipated as the result of more careful experimental work based on adequate anatomical controls. That some type of functional localization does exist in the cerebrum and cerebellum is not to be doubted, but, at least so far as the "visceral brain" is concerned, its anatomical

basis is still much too uncertain to provide a satisfactory rationale for treatment by selective surgical ablations.

Professor Fulton's book provides a useful summary of the recent physiological studies of the frontal lobes and cerebellum and is made additionally attractive by its historical references.

W. E. LEGROS CLARK.

INDIVIDUAL AND SOCIETY

Social Psychology and Individual Values. By D. W. Harding. (Pp. 184. 8s. 6d.) London: Hutchinson's University Library. 1953.

Professor Harding sets out to be of use to readers whose interest is chiefly in the "implications of Social Psychology for the broader concerns of social life and culture." But the book is small and this is too large a target. Unfortunately, too, the language is that of the lecture room—clear enough to students of psychology but obscure to others. Nevertheless the book contains first-rate material, particularly in the discussions on individual and social values. The need for the individual to "adjust" himself to his society has had more than enough prominence in psychological and sociological literature. Harding argues that Western societies have valued too highly the individual's contribution to the material prosperity of the group, in spite of the lip-service paid to other values, such as art, scholarship, religion, social wisdom, moral development. Inevitably this leads to an over-emphasis on the middle period of life—that is, the period of fertility in woman and material productiveness in men. So childhood is viewed as a preliminary and old age as an aftermath of the golden age of productivity. The values and interests that outlast middle life are neglected and cannot be acquired overnight. The second half of life has a significance beyond the earning of money and the furtherance of ambitions. But having been told that "the loss of function in old age is a problem of the communities' scale of values," we are left to speculate on how the community can set about altering this state of affairs. The problem is really one for each individual, and, ideally, should never arise. The chapter on leadership is excellent, the leader—as opposed to the boss—being depicted as one who co-ordinates the efforts of a number of people and who is not notably concerned in building up his own status.

E. A. BENNET.

HEPATIC CIRCULATION

The Hepatic Circulation and Portal Hypertension. By Charles G. Child, III, M.D., in collaboration with 11 doctors from Department of Surgery and the Laboratory of Surgical Research of the New York Hospital, Cornell Medical Center. (Pp. 444+xiii; 132 figures. 60s.) London and Philadelphia: W. B. Saunders Company. 1954.

It is difficult to do justice to this excellent book within the limits of a review. Dr. Charles Child has collected into one volume all that is known about the liver, about its structure, its functions, and its circulation. He gives a summary of the earliest writings on the subject and an account of the comparative anatomy and embryology of the hepatic circulation. He discusses in detail the experimental work, much of which is his own or that of his associates, on the minute and gross anatomy of the hepatic vasculature, including a schematic reconstruction of the architecture of the hepatic lobule. The later part of the book is devoted to a consideration of portal hypertension and its treatment.

There is so much important work within these pages that a detailed survey is impossible. Chapter X, on the effect of liver disease upon body water, a chapter of ten pages only, contains an illuminating discussion on the relation of ascites to portal hypertension, and makes it clear that the relationship is not the simple one of transudation due to back pressure, but that many questions still remain to be answered. In Chapter XV the author describes the operation of pancreatico-duodenectomy with resection of the portal vein which he has devised, after proving by animal experiments that it could be done, and which he has performed four times without an operative death.

The book is clearly written and well produced. The illustrations are admirable. Dr. Child has given us a study that will prove equally valuable to the clinician and the scientist: to the clinician in making available and intelligible the great mass of research work that has been done on the physiology and pathology of the hepatic circulation, to the research worker in giving him an insight into the clinical problems associated with liver disease, and the many uncertainties that yet remain to be cleared up.

HENEAGE OGILVIE.

CARDIAC ARRHYTHMIAS

Clinical Disorders of the Heart Beat. By Samuel Bellet, M.D. (Pp. 373; 164 illustrations. 63s.) London: Henry Kimpton. 1953.

A fresh appraisal of the cardiac arrhythmias has been made necessary not only by the new operations upon the heart and by procedures such as cardiac catheterization, but also by the advances that have been made in pharmacology and therapeutics. In this book Dr. Samuel Bellet has produced exactly what physicians, and cardiologists particularly, have needed for several years. The work is divided into sections on physiology and general therapeutics, on the individual arrhythmias, on the arrhythmias in certain clinical states, and a review of the drugs used in the treatment of arrhythmias. While in the clinical sections as well as in those on therapy the author discusses various hypotheses, he gives his own opinion unequivocally. Moreover, he clarifies each chapter by excellent synopses. How greatly the knowledge of the mechanism of the heart beat and its control has been advanced in recent years is shown by turning the pages of this monograph. The roles of neurogenic disorders and of metabolic dyscrasias in the causation of arrhythmia are discussed as well as the regulating influences of electrolytic and endocrine balance. Any experienced physician will admit that certain disorders of the rhythm of the heart present some of the most pressing and difficult problems among the cardiac emergencies. The author has faced these issues and given sound general advice in addition to the practical details of treatment.

A selection at random of the chapters of this work may help to indicate its scope: anaesthesia and surgery, cardiac arrest, the occurrence of ectopic rhythms in cardiac catheterization, the arrhythmias following cardiac trauma, the mechanisms underlying syncopal attacks, the use of procaine amide, paroxysmal tachycardia, and the effect of arrhythmias upon the ballistocardiogram—these give some idea of the range covered. Dr. Bellet has brought his wide experience and skill to a complex and exacting task. He has produced a balanced, well-documented, and readable survey of his subject. I know no better one on this theme.

K. SHIRLEY SMITH.

Among new editions of well-known books that have appeared recently is the second edition of Dr. R. I. S. Bayliss's *Practical Procedures in Clinical Medicine*. Intended chiefly for house-men and general practitioners, this introductory manual describes many procedures in chemical pathology and minor surgery for the investigation and treatment of patients. The book has been extensively revised in the light of recent developments and a a table of normal values has been added. It is published by J. and A. Churchill Ltd. for 32s.

For the second edition of *Modern Practice in Anaesthesia* (Butterworth & Co. Ltd., 65s.) the editor, Dr. Frankis T. Evans, has had to omit parts of the first edition in order to make room for the large quantity of new material. The text has also been revised throughout.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY SEPTEMBER 18 1954

RETROLENTAL FIBROPLASIA

Experimental work has recently thrown fresh light on the cause of incurable bilateral blindness in premature infants, particularly those whose birth weight is in the region of 3 lb. (1.3 kg.). This disorder, retrolental fibroplasia, has appeared within the preceding decade in many countries throughout the world, particularly in Great Britain and America. Its pathology has been established as a proliferation of the retinal vessels into the vitreous, followed by fibroblastic changes, until eventually in a fully developed case the newly formed fibrous tissue detaches the retina and stretches as a solid sheet behind the lens, but the aetiology was by no means clear when the subject was discussed in these columns a year ago.[1] Attention was then drawn to the publication of preliminary experimental work undertaken by Ashton and his associates at the Institute of Ophthalmology in London.[2] Experimenting on the kitten, an animal chosen because the stage of development of its retinal vasculature corresponds very closely with that of the premature infant, Ashton and his colleagues found that if these animals were kept for several days after birth in conditions of hyperoxia the developing retinal vessels became obliterated; on return to air, new vessels grew from the disk not in an ordered network but as an exuberant irregular system preceded by haemorrhages, not confined to the retina but proliferating freely into the vitreous, exactly as occurred in the early stages of retrolental fibroplasia.

These workers have recently published a full report of their elaborate experimental researches,[3 4 5] in which the whole series of events in the eye of the kitten has been observed clinically and studied pathologically. As a controlled series of biological experiments this work is of an unusually high order. When the kitten is exposed to high concentrations of oxygen in the first few days of its life an initial and marked vasoconstriction appears after some five minutes and lasts some ten minutes, after which time the vessels reopen. About eight hours' exposure is followed by a total obliteration of the retinal circulation, affecting even the larger vessels, so that the retina is virtually deprived of its blood supply. If anticoagulants had been administered, the retinal circulation reopened when the animals were transferred to air; but, without these, the vaso-obliteration became irreversible after about 36 hours. On exposure again to air the retina revascularized anew from the disk in the profuse and uncontrolled manner already described. The extent of these changes varies directly with the concentration of oxygen; 70 to 80% of oxygen is invariably effective in their production, and concentrations below 35% have few or no ill effects. The changes thus produced are exactly parallel with those seen in the early stages of all cases of clinical retrolental fibroplasia and they remain so with the non-progressive cases of this disease. The fibroblastic sequel causing retinal detachment seen in progressive cases does not occur in the kitten, for in this animal the vessels proliferating into the vitreous gradually disappear and the vision remains normal. The two essential steps in the experimental disease are therefore shown to be an initial vaso-obliteration induced by hyperoxia and a subsequent vaso-proliferation in the state of retinal anoxia when a return is made to air. It is interesting that somewhat similar changes, milder in degree and confined to the retina, can be induced if young kittens are kept in low concentrations of oxygen (10 to 15%), when the phase of vaso-obliteration and therefore the extreme relative anoxia on transference to air do not occur. This experimental work has recently received confirmation from Stockholm, where Gyllensten and Hellström[6] have found that substantially the same changes can be induced in the eyes of newborn mice subjected to 98–100% oxygen.

These results are of unusual interest. The second stage of vaso-proliferation is presumably a reaction to the anoxic state; the cause of the initial vasoconstriction is much less clear. The effect in the kitten is seen only while the retinal vessels are at a particular stage of development; the vessels are most susceptible in the first 14 days of life when they are growing just beyond the equator of the globe; 21 days after birth the phenomenon is not seen. Fully developed vessels, as in the hyaloid system, are unaffected. Moreover, developing vessels in the adult animal, as in the cornea or the rabbit ear chamber, show no such response; but any similar effect of oxygen on the developing vessels in other situations in the

1 *British Medical Journal*, 1953, **2**, 610.
2 *Brit. J. Ophthal.*, 1953, **37**, 513.
3 Ibid., 1954, **38**, 385.
4 Ibid., 1954, **38**, 397.
5 Ibid., 1954, **38**, 433.
6 *Acta paediat. (Uppsala)*, 1954, **43**, Suppl. 99. In press.
7 *Amer. J. Ophthal.*, 1951, **34**, 1649.
8 Ibid., 1952, **35**, 1248.
9 *Med. J. Aust.*, 1951, **2**, 48.
10 *Amer. J. Ophthal.*, 1952, **35**, 329.
11 *Arch. Dis. Childh.*, 1952, **27**, 329.
12 *Arch. Ophthal. (Chicago)*, 1952, **48**, 83.
13 Forrester, R. M., *et al.*, *Lancet*, 1954, **2**, 258.
14 Gordon, H. H., *et al.*, *Bull. Johns Hopk. Hosp.*, 1954, **94**, 34.
15 Locke, J. C., *Arch. Ophthal. (Chicago)*, 1954, **51**, 73.
16 Lanman, J. T., *et al.*, *J. Amer. med. Ass.*, 1954, **155**, 223.

mammalian embryo is unexplored. Ashton and his colleagues found that if a retinal detachment was induced the obliterative effect was not seen in this area even though it was evident in portions of the same retina that remained attached. This suggests either that hyperoxia contributed by both the retinal and choroidal circulations is necessary, or that some vaso-obliterative substance is elaborated in the choroid. Unless the retinal vessels at a specific and limited stage of their development possess a peculiar and (apparently) unique reaction to oxygen, the question arises whether some vasoconstrictive substance is elaborated in the retina or the surrounding tissues owing to the disturbance of the metabolism caused by an excess of oxygen. The oxidative metabolism of the retina is largely unknown, but it has been established that its powers of anaerobic glycolysis are equalled only by those of neoplastic tissue. The explanation of these phenomena therefore raises questions of unusual interest, the solution of which may explain the peculiar reaction of the retinal vessels in many systemic diseases and may throw new light on capillary growth in general.

From the practical point of view the lessons to be drawn from this experimental work are more immediately apparent, and, indeed, have already borne fruit. The excessive administration of oxygen in premature nurseries, a habit doubtless fostered by the subsequent ease of nursing, has for some time given rise to suspicion, and reports such as those of Szewczyk[7] and Patz *et al.*[8] from America, Campbell[9] and Ryan[10] from Australia, and Jefferson[11] and Crosse and Evans[12] from Britain drew attention to the fact that the incidence of this disease fell rapidly when oxygen was administered only in small amounts to recently born infants. During the present year reports of an even more dramatic nature have been appearing. Thus in Manchester retrolental fibroplasia, which previously had a notably high incidence, has completely disappeared since the use of oxygen was severely restricted in October, 1951.[13] In Johns Hopkins Hospital no permanent ocular changes have been observed since the concentration of oxygen has been cut down to or below 40%.[14] A similarly striking fall in incidence has been reported from Montreal.[15] At the Bellevue Hospital an interesting control series was run[16]: among 36 surviving infants who were nursed with 70% oxygen, eight cases of retrolental fibroplasia occurred, six of the infants being blind, while no case occurred among 28 surviving infants nursed with 40%. These figures speak for themselves, and it is of importance that the reduction in oxygen has in no case had a deleterious effect upon the survival rate.

It would be rash to attribute the entire effect to the inhalation of oxygen; doubtless other factors such as severe illness or debility, hormonal imbalance, or metabolic disturbance may well act as adjuvant factors. Moreover, sporadic cases of retrolental fibroplasia were seen before the last decade and also still occur occasionally when oxygen has been given with care. It is possible that such cases may be due to anoxic conditions alone, occurring perhaps in intrauterine life. But there seems little doubt that retrolental fibroplasia appearing as a common endemic catastrophe in nurseries for premature infants can be virtually eliminated provided oxygen is administered only when it is necessary for the survival of the child, and then for as short a time as possible, and only in effective concentrations below 40%.

TIN AS A POISON

Those who are inclined to attribute some of the ills of civilized man to the quality of the food he prepares for himself have rarely included tin in their strictures. The tin can has been successfully used for food preservation on a vast scale for a century. In many instances military and civil expeditions have existed for long periods almost entirely on canned food and no ill effects have ever been attributed to the tin that they have consumed. Tin is certainly present in most, if not all, tinned food in concentrations of 20–50 p.p.m. With all the modern emphasis on the supposed necessity for extensive investigations with laboratory animals on the toxicity or non-toxicity of any chemicals deliberately or accidentally added to food, it is interesting that the evidence for the innocuity of tin rests upon experiments on a few cats[1] and dogs.[2] The permitted limits for tin in food appear to be determined by the maximum likely to be found and bear no apparent relation to any amount that might be thought toxic.

Tin is generally considered to be a metal whose simpler compounds, when ingested, lack toxic properties. It seems not to cause any particular occupational disease; indeed, it has been stated that tin workers show a remarkable freedom from furunculosis. This tradition led to French work, published in 1917,[3 4] claiming not only that tin and tin salts

[1] Lehmann, K. B., *Arch. Hyg.* (*Berl.*), 1902, **45**, 88.
[2] Schryver, S. B., *J. Hyg.* (*Lond.*), 1909, **9**, 253.
[3] Grégoire, R., and Frouin, A., *Bull. Acad. Méd.* (*Paris*), 1917, **77**, 704.
[4] Frouin, A., *Presse méd.*, 1917, **25**, 402.
[5] Kolmer, J. A., *et al.*, *J. Pharmacol.*, 1931, **43**, 515.
[6] Hazard, R., *Précis de Thérapeutique et de Pharmacologie*, 9e Edit. Paris, 1950.
[7] Reitler, R., and Marberg, K., *Trans. roy. Soc. trop. Med. Hyg.*, 1943, **38**, 305.
[8] White, T. R., *Arch. exp. Path. Pharmak.*, 1881, **13**, 53.
[9] Ungar, E., and Bodländer, G., *Zeit. Gew. Hyg.*, 1887, **2**, 241.
[10] *Pharm. J.*, 1954, **173**, 54.
[11] Rouzaud, M., and Lutier, J., *Presse méd.*, 1954, **62**, 1075.
[12] van der Kerk, G. J. N., and Luijten, J. G. A., *J. appl. Chem.*, 1954, **4**, 314.

modified the virulence of staphylococci cultured in the laboratory but that, when administered by mouth, they could cure the condition of furunculosis. Tin and its oxides were the compounds used, and they have figured in pharmacopoeias and textbooks of treatment ever since. In 1931[5] American investigations failed to confirm the value of tin compounds in treating skin infections, so that in American textbooks tin rarely receives a mention. The *British Pharmacopoeia* states that tin compounds are of doubtful value in treatment of furunculosis. Tin oleate survives in one textbook as a treatment for eczema of the nails. A recent French treatise is much more enthusiastic about the value of simple tin compounds in furunculosis.[6] A long paper[7] from Palestine claimed that tin suspended in tin stearate was of value in the treatment of typhoid, though the paper itself provides little evidence for this claim. Tin is also a discarded treatment for epilepsy. The reports on the use of tin in therapy emphasize that it is non-toxic, and there is indeed little reason to doubt that the simple salts are. But evidence of the extreme toxicity of certain tin compounds is not lacking, and papers describing the toxic effects of small quantities of tri-ethyl tin salts were published about seventy years ago.[8,9] Weakness, paralysis, and convulsions were seen in a variety of animal species given tri-ethyl tin salts by mouth or by injection.

In France enthusiasm for tin compounds in treating furunculosis persists, and recently an organic compound of tin (di-ethyl tin diiodide combined with linoleic acid, or "vitamin F") was put on sale and apparently widely prescribed. So far it is believed that over 50 people have died before the cause of their fatal illness was traced to this new therapeutic preparation.[10] Details of one case have been published[11] and show that the condition may be protracted, with severe headache, disorientation, and transient signs of an organic cerebral lesion; it was believed to be a case of cerebral abscess secondary to the furunculosis for which the tin had been given. The fatal cases are said to have suffered from encephalopathy, which is indeed what might have been expected if man responded in the same way as animals to these ethyl tin compounds. It is possible that this disastrous French experience may have been stimulated by recent work showing that certain organic compounds of tin possess powerful fungicidal properties.[12] This is not the first time that simple alkylated compounds of heavy metals have produced serious and even fatal human poisoning; tetra-ethyl lead and methyl mercury salts are two well-known examples.

The possible hazards from the use of such compounds have been only too well illustrated by events in France. Tin metal and its simpler compounds clearly do not possess these toxic properties, for the widespread use of preparations containing them in the treatment of furunculosis has in past years earned for them a reputation for harmlessness, if perhaps little else. The same is almost certainly true of the tin found in food. But the time is ripe for further work on the toxic properties of organic tin compounds. It is to be hoped that fuller clinical details of the French cases will be published so that experimental work may be directed towards the more interesting and significant facets of the problem.

PILONIDAL SINUS

The condition now known as pilonidal sinus was first described by Anderson in 1847,[1] but it was not for many years that it was clearly recognized as a disease distinct from fistula-in-ano. Writing as late as 1917, Sir John Bland-Sutton[2] emphasized the need to make this distinction in diagnosis. Like all other writers until very recent years, Bland-Sutton stated that the condition of pilonidal sinus arose as a result of a developmental error in this area, and believed that it was due to a faulty coalescence of skin in the midline, resulting in an inclusion dermoid. Other workers, notably Mallory,[3] believed that the condition developed from caudal remnants of the medullary canal. Proponents of both these points of view agreed that the congenital defect lay dormant until it became infected, and further that as a result of this inflammation the epithelial lining of a varying portion of the cyst was destroyed, thus explaining why, in many cases, the greater part of the track is lined by granulation tissue.

However, there are a number of facts which are difficult to explain by either theory of congenital origin. Uninfected dermoid cysts in the post-anal region are very rare, and it is by no means clear why a congenital lesion should predominantly affect the male sex and manifest itself only in the second and third decades of life. Further, while the tracks frequently contain hair, this is practically never attached to the walls of the sinus, and neither hair follicles nor sebaceous glands are commonly found in these walls.[4] These arguments were stressed by Patey and Scarff,[5] who further pointed out that the histology of a recurrent pilonidal sinus is identical with that of the primary lesion, even in cases where the original excision was such as to preclude the possibility that recurrence was due to a remnant of the original sinus.

Accordingly they suggested that a pilonidal sinus is not congenital in origin, but is an acquired sinus resulting from a foreign-body reaction round hairs which enter from the neighbouring skin. In support of this view they reported a case of pilonidal sinus occurring in the interdigital web of a barber's hand; more recently further similar cases have been recorded,[6 7] and Aird[8] has reported a case occurring in the axilla. If this theory is correct, it is easy to understand why the condition predominantly affects those with profuse, strong body-hair, why it is more commonly seen in men than in women, and why it is apt to occur two to three years earlier in women than in men, in accord with the earlier onset of puberty in the female. It is not clear whether entry of hair through the skin is the primary event or follows a small abscess, but Patey and Scarff[5] point out that the lesions are found only in clefts of skin, and suggest that in such situations movement may set up suction forces which cause deep penetration by hairs, later followed by infection.

Undoubted congenital lesions do occur in the post-anal region in the form of sacro-coccygeal teratomata, which lie in the hollow of the sacrum and present as tumours bulging into the posterior wall of the rectum. Again, rare cases are seen in which caudal remnants of the original neural canal survive, but these are usually found in the lumbar region and are definitely connected to the spinal theca. However, both these conditions are clearly distinct from pilonidal sinus. It may well be that in the latter condition small congenital pits play a part in initiating the lesion, but the weight of evidence suggests that essentially it is an acquired lesion.

In a recent paper Dwight and Maloy[9] discuss this new concept of the aetiology of pilonidal sinus, and consider its implications for treatment. In the past emphasis has been laid on the importance of wide excision of the lesion, so as to avoid recurrence from overlooked remnants of the "congenital" track. This procedure necessarily leaves a deep wound with rigid sides, presenting awkward problems in obtaining rapid healing. If the wound is left to granulate sound healing can be obtained, but this is a slow process and many operations have been described which are designed to obliterate the dangerous dead space and so allow of successful primary suture, and in an attempt to shorten the time of healing many techniques of closure have been tried out. Thus Shute *et al.*[10] described an ingenious operation involving the use of double flaps of the gluteus maximus, and reported that 90% (of 57 cases) healed without complication in an average time of eight days. However, the multiplicity of operations suggests that no single one is dependable, and all suffer from the disadvantage that if breakdown occurs secondary healing is then likely to take longer than if no attempt had been made to suture the wound.

In their paper Dwight and Maloy[9] conclude that "an extensive plastic procedure . . . is not a justifiable method of treating pilonidal sinus," and recommend simple incision and packing for all but very small lesions. These authors point out that it is unnecessary to remove the entire track, and that all that is required is to lay open the track and its ramifications. This point was stressed earlier by Buie,[11] who reported satisfactory results from splitting open and marsupializing the tracks. The rationale of wide, complete excision was based on the theory that a pilonidal sinus is a congenital lesion. If this belief was incorrect it is only logical to question the therapy it led to. All surgeons would agree that extensive excision results in wounds which can be closed only with difficulty, and in the light of recent evidence it seems that the necessity for such wide ablations is doubtful. If pilonidal sinus is an acquired condition, then indeed no such radical procedure is required. The tracks must be laid open fully, with removal of all hair and other debris, but the minimum of tissue should be excised and the infected wounds left to heal by secondary intention. Perhaps marsupialization or, in selected cases, primary suture will expedite healing, but in general it seems that the wheel has come full circle, and that once again success in the treatment of this condition will depend on the correct design and care of an open wound.

[1] *Boston med. surg. J.*, 1847, **36**, 74.
[2] *Tumours Innocent and Malignant*, 7th edition, 1922, London, Cassell & Co., Ltd.
[3] *Amer. J. med. Sci.*, 1892, **103**, 263.
[4] Kooistra, H. P., *Amer. J. Surg.*, 1942, **55**, 3.
[5] *Lancet*, 1946, **2**, 484.
[6] Ibid., 1948, **2**, 13.
[7] Ewing, M. R., ibid., 1947, **1**, 427.
[8] *British Medical Journal*, 1952, **1**, 902.
[9] *New Engl. J. Med.*, 1953, **249**, 926.
[10] *Ann. Surg.*, 1943, **118**, 706.
[11] *Sth. med. J. (Bgham, Ala.)*, 1944, **37**, 103.

USES OF BLOOD FRACTIONS

The separation of plasma proteins by ultracentrifuge and electrophoresis has enabled us to distinguish clearly between the different protein molecules, and with their help the fractionation of plasma has been put on a new and more scientific basis. In 1908 Mellanby[1] showed that ethanol could be used to precipitate antitoxic protein from anti-diphtheria toxin horse serum without loss of activity, provided that the temperature was maintained at 2° C. Since then technological advances in mechanical refrigeration have facilitated the development of

freeze-drying methods.[2] A procedure in which organic solvents were used as precipitants was shown to be a practical proposition by Professor Cohn and his collaborators.[3] As the solvents are bacteriostatic, aseptic conditions can be more easily achieved, and at the end they can be removed from the protein by freeze-drying under sterile conditions. During the last war blood occasionally accumulated in excess of what was needed for immediate transfusions. No methods were available then to preserve the red cells for more than two to three weeks, but preservation of plasma was practicable. When kept as a solution a precipitate developed similar to that from bacterial contamination; it was shown to be due to the separation of insoluble lipid.[4] McFarlane[5] showed that most of the lipid was removed by freezing the protein with ether at −25° C. Thus, when Cohn and his team[6] at Harvard produced concentrated human albumin solutions of great stability using ethanol, in Britain similar efforts were made with ether fractionation.

In 1943 the Blood Products Research Unit was set up jointly by the Medical Research Council and the Lister Institute, and Drs. R. A. Kekwick and M. E. Mackay have now published a report on the separation of protein fractions from human plasma with ether.[7] There are four main groups: the proteins associated with the clotting mechanism, the alpha and beta globulins, the gamma globulins, and the albumins. Of these, fibrinogen and thrombin, gamma globulin, and albumin have been produced over the last ten years in consistently pure form and in good yield. There is little doubt that the alpha and beta globulins will in future be used for the preparation of many compounds of possible clinical value. In these fractions would be found most of the plasma enzymes, such as amylase, phosphatases, caeruloplasmin—a copper-containing oxidase of beautiful blue colour which is deficient in cases of hepato-lenticular degeneration (Wilson's disease)—and the pseudocholinesterase to which attention has recently been drawn by work on prolonged apnoea after treatment with suxamethonium.[8] In the treatment of burns fibrinogen and thrombin have been used to form a film of fibrin to cover the denuded surfaces. However, Macfarlane[9] has not found this treatment satisfactory, and thinks that the plasma required for this purpose would be better administered as a transfusion. More emphatic was the favourable reception of suitable mixtures of fibrinogen and thrombin for skin grafting, in which they are used as an adhesive to hold the graft in place. Fibrinogen has also been used to hold nerve fibres during nerve-grafting operations. Clotted and plasticized fibrin has been pressed into sheets and been applied in the repair of dural defects. These materials are absorbed by the body at rates ranging from five days for untreated films to eighty days for fully plasticized material. Fibrin foam soaked in thrombin has been used as a haemostatic in the surgery of the nervous system and of the lung, and for miscellaneous purposes such as arrest of haemorrhage in liver biopsy and in operations on the liver, spleen, and pancreas. When the blood from bleeding-points comes into contact with the large surface area of the foam it will be exposed to relatively large amounts of thrombin acting as a clotting agent.

The antihaemophilic globulin is contained in the fibrinogen fraction. However, fresh plasma transfusion is still preferred for the treatment of haemophilia. This is owing partly to the instability of the antihaemophilic globulin—the yield of active fraction by precipitation drops sharply when plasma is stored—and partly to the recognition of new antihaemophilic proteins, at least one of which, plasma thrombin component (P.T.C. or the Christmas factor), is now known to be a beta globulin.

Numerous antibodies are associated with the gamma globulins. Those against measles, poliomyelitis, and infective hepatitis have been extensively studied, though the high hopes entertained for the prevention of poliomyelitis by gamma globulin seem to have been disappointed. Again, the value of gamma globulin in suppression of German measles is questionable. In infective hepatitis, as in measles, the attack can be suppressed or attenuated, while the incubation period is unaltered; in homologous serum jaundice the incubation period is prolonged, though the character of the attack is not affected. Albumin finds its place primarily in combating shock and restoring plasma volume. Perhaps recent work[10] on kernicterus in infants may lead to a procedure by which free circulating bilirubin is mopped up by injection of albumin. Professor N. H. Martin has contributed an addendum to this report on the use of albumin transfusion in diseases associated with low circulating albumin. Its relatively low viscosity and low sodium content are advantageous when massive transfusions of protein in a restricted fluid bulk are needed, and Professor Martin was able to give 800 g. in a single 14-day course to selected patients.

The decision to give blood or plasma transfusions should never be taken lightly if only because of the risk of infecting the recipient with homologous serum jaundice. Albumin and fibrin foam are heated to inactivate the infective agent, but all other fractions may be contaminated. Drs. Kekwick and Mackay were able to compare a batch of plasma which proved to be icterogenic with the gamma globulin prepared from this pool. The plasma caused jaundice in seven out of ten cases; the gamma globulin was injected into fifty-eight recipients (one of whom received 2,500 mg.), and only one of these, a boy of 12 who had received 600 mg. of globulin, became infected, a mild jaundice occurring 74 days after the injection. As these authors say, this lowering of the risk of subsequent serum hepatitis in itself makes the labour of fractionation worth while.

[1] *Proc. oy. Soc. B*, 1908, **80**, 399.
[2] Greaves, R. I. N., and Adair, M. E., *J. Hyg. (Lond.)*, 1939, **39**, 413.
[3] *J. Amer. chem. Soc.*, 1940, **62**, 3396.
[4] Francis, G. E. C., *et al.*, *Lancet*, 1944, **1**, 51.
[5] *Nature (Lond.)*, 1942, **149**, 439.
[6] *J. Amer. chem. Soc.*, 1946, **68**, 459.
[7] *The Separation of Protein Fractions from Human Plasma with Ether*, 1954, *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 286.
[8] Evans, F. T., *et al.*, *British Medical Journal*, 1953, **1**, 136.
[9] Ibid., 1943, **2**, 541.
[10] Claireaux, A. E., *et al.*, *Lancet*, 1953, **2**, 1226.

TEMPORARY LEUCOTOMY

The value of prefrontal leucotomy in the treatment of certain psychoses and neuroses and of some patients with intractable pain is now firmly established. It has, however, become obvious that after the standard operation the frontal-lobe syndrome develops in varying degree with effects often far more obvious to the patient's family than to his doctors. Especially important among these undesirable effects of the operation are emotional dulling with loss of initiative; reduction of abstract thinking and synthesis with deterioration in judgment and ability to plan; and a diminished social responsibility with lack of tact and quarrelsomeness. Various modifications of the standard leucotomy operation have been introduced with the intention of gaining the desired therapeutic effect while minimizing the unwanted sequelae, but even with such conservative surgery the personality change may be marked while pain or mental symptoms remain little altered.

A pre-operative test to demonstrate the effects which leucotomy will produce in any individual patient would have great value, and a number of studies have been made with this end in view. It has been shown that in animals nerve pathways in the cerebral hemisphere may be temporarily blocked by means of injection of local anaesthetic solutions without the production of pathological change.[1] The effects of the injection of similar solutions into the white matter of the frontal lobes through leucotomy burr openings have been observed in patients in whom the operation failed to bring benefit. Such injections produced temporary improvement—a finding which points to the inadequacy of the original operation. Putnam[2] has injected into the frontal white matter on both sides 1 to 2 ml. of a 10% solution of procaine in iodized sesame oil through cannulae introduced transorbitally. He has found the injections of some prognostic value and at times their effects have been prolonged. Van Wagenen[3] has introduced 3 ml. of 2% procaine into the frontal white matter bilaterally through burr openings—taking precautions to ensure previous obliteration of the subarachnoid space. The injections were repeated upon a number of occasions in some patients and are reported as being successful in the treatment of borderline cases. Grant and others[4 5] have used a similar technique to render inaccessible patients suitable for psychotherapy and record benefit from this approach. They consider that the personality change seen after leucotomy may thus be reduced. They have also investigated the value of frontal procaine injections in cases of intractable pain where the patient's life expectancy is short and where interruption of a single pain pathway would prove inadequate to deal with multiple sources of misery. As much as 30 ml. of 2% procaine has been injected into the frontal white matter—the actual quantity being determined by the effect of the injection in producing euphoria, disorientation, and so on. They have found that confusion passes in a few hours and that there is no complaint of pain for two to three days: some patients remained comfortable for four to nine weeks. The injections can be repeated as required, the procedure being carried out in the patient's bed under local anaesthesia. Among the ill effects recorded are epilepsy and hyperpyrexia.

More investigations must be carried out before the value of temporarily blocking the fronto-thalamic pathways by these injections can be established. They might be particularly useful in the relief of intractable pain and for patients in whom something less than a leucotomy, with its risks of sequelae, is desired. The blind nature of the procedure makes its value as a pre-leucotomy test questionable. While the search for a form of psychosurgery which will relieve the patient without producing a deterioration of personality must continue, it should be borne in mind that the actual leucotomy can be varied only quantitatively and not qualitatively, and that similar lesions will not produce similar effects in different patients. Further, alteration in personality may be unavoidable in certain patients if symptoms based on emotional tension are to be relieved.

[1] Lindsay, J. S. B., *J. ment. Sci.*, 1950, **96**, 923.
[2] *Trans. Amer. neurol. Ass.*, 1950, **75**, 125.
[3] *J. Neurosurg.*, 1952, **9**, 30.
[4] *J. Amer. med. Ass.*, 1953, **153**, 1016.
[5] *Arch. Neurol. Pyschiat. (Chicago)*, 1953, **69**, 653.

"ANNALS OF THE RHEUMATIC DISEASES"

It is not far short of twenty years since the appearance of the first annual report of the British Committee on Chronic Rheumatic Diseases, set up by the Royal College of Physicians in 1934. Four of these annual reports were issued, and then in 1939 a new quarterly journal took their place. Given the title of the *Annals of the Rheumatic Diseases*, it was published under the aegis of the Scientific Advisory Committee of the Empire Rheumatism Council. It was natural that the committee should select Dr. C. W. Buckley as editor, for he was largely responsible for making the reports of the British Committee on Chronic Rheumatic Diseases such a valuable and lasting contribution to the literature on rheumatism. From 1939 to the end of last year Dr. Buckley has put all his great experience and knowledge into editing the *Annals of the Rheumatic Diseases*, the publication of which was taken over by the B.M.A. in 1944. During his editorship the *Annals* became the leading rheumatological journal in the world, and it has the support of numerous international organizations. At the beginning of this year he was succeeded as editor by Dr. W. S. C. Copeman, who was one of his original helpers when the *Annals* was first started. The current issue, published this week, contains an editorial tribute to Dr. Buckley on his eightieth birthday, which will be on October 10, and it is fitting that the opening article by Dr. F. Dudley Hart should be on the subject of ankylosing spondylitis, a disease which Dr. Buckley's own careful and long-continued observations have done much to elucidate. Readers of the *Annals of the Rheumatic Diseases* and friends of Dr. Buckley—not only in Buxton, where he has lived and practised for so many years, but all over the world—will hope to see the journal and its former editor continue to thrive for many years to come.

POLIOMYELITIS

INTERNATIONAL CONFERENCE IN ROME

[FROM A SPECIAL CORRESPONDENT]

The Third International Poliomyelitis Conference was held in Rome from September 6 to September 10. The first conference, held in New York in 1948, commemorated the tenth anniversary of the National Foundation for Infantile Paralysis. At the second, held at Copenhagen in 1951, the demonstration that poliomyelitis virus could be cultivated on extraneural tissues, that a complement-fixation test was possible, and that the Coxsackie groups of viruses might mimic poliomyelitis were the highlights. This year's conference was officially opened in the City Hall by the Mayor of Rome. The opening session, on "Social Aspects of Poliomyelitis," was held at the Orthopaedic Clinic of the University.

Social Aspects of Poliomyelitis

Professor S. CRAMAROSSA (Rome) said that, despite financial depression in Italy, the State had been saddled with unlimited responsibilities for patients with poliomyelitis, which in 1939 when there was an epidemic of 600 cases had cost 3m. lire; in 1953 when there had been 4,980 cases the cost had risen to 1,000m. A repercussion of this special legislation was public apathy and lack of co-operation by patients. His aim was to return all attacked to work at the earliest possible moment. Wherever possible education should be continued in the ordinary schools and employment should be at the same trade as before illness; if a new occupation was needed, it was better to train for a handicraft, producing fine work, than for a factory job producing cheap objects. True rehabilitation meant that the poliomyelitis patient could compete with the able-bodied at his own work.

Dr. SVEN M. CLEMMESEN (Denmark) said that long-term rehabilitation was a national affair, but Denmark, Finland, Iceland, Norway, and Sweden shared doctors, nurses, and physiotherapists, prophylactic facilities, and finances during epidemics. The State provided economic support for the families of disabled housewives during their rehabilitation. Reduction in mortality could mean an increase in those with severe limb paralysis, and a register of them and of those who as growth progressed were liable to develop scoliosis was being prepared to ensure adequate provision for the future. He emphasized the frequency of psychological reactions in badly treated patients.

Dr. CHESTER S. KEEFER (U.S.A.) stated that for total control an informed public was essential. Health authorities could put out accurate statements by press, radio-television, and public meetings. Rehabilitation was greatly rewarding, but it was costly, and an ever-increasing number of the population were insuring against the risk, $5 being the premium for an individual and $10 for a family for cover up to $5,000. In the discussion Dr. R. MACKINTOSH (New York) said one of the wider social problems was the reaction of the community and profession to the disease. With the limited means for immediate diagnosis, in epidemics too many and in non-epidemic times too few cases were correctly diagnosed. Others spoke of the value of clubs for young and old, the need for efficient transport, and the importance that education should be as normal as possible.

The afternoon session was devoted to reports from official (government) delegates. Many were along standard lines—that the countries concerned were being attacked more frequently, that the shift from infantile to adolescent and adult was noticeable, that bulbar cases were increasing, and that boys were attacked more than girls, this last opinion being expressed several times. In Norway the proportion of paralytic to preparalytic cases was high—that is, 1,563, 507, and 838 paralysed in 1951, 1952, and 1953 respectively, against 670, 192, and 189 preparalytic cases, a phenomenon which might be important in view of the opinion expressed elsewhere that patients in Denmark and Sweden in 1952 and 1953 had had unusually severe manifestations. Contrariwise, there were no epidemiological problems in Lebanon, where children have high antibody titres.

Treatment of the Acute Stage

Dr. A. J. RHODES (Canada), opening the session on "Acute Medical Care in Poliomyelitis," discussed the diagnosis of a disease which in its early stage simulated many other fevers. The abortive form must be suspected in children with fever, headache, sore throat, gastro-intestinal upsets, etc. The preparalytic or meningitic and the paralytic stages might follow. He believed lumbar puncture should be routine: it excluded bacterial infections. The average cell count was 150 per c.mm., with limits of 10 to 500, and of these 50% were polymorphonuclear. Mumps, which caused 10% of their admissions, had counts averaging 400 (80% lymphocytes), and lymphocytic choriomeningitis counts of 700, and protein of 100 mg. per 100 ml., whereas in poliomyelitis it was insignificantly raised. In the laboratory diagnosis he included culture of the organism on extraneural tissues. In 85 of 95 cases tested it had been successful in producing "cytopathogenic reactions"—that is, destruction of cells from embryonic skin, kidney, etc. This was on the first attempt, and included inocula of faeces, blood, or throat washings. The cytopathogenic changes were nonspecific and had been observed in infections with herpes, Coxsackie, and allied viruses. Nevertheless, he believed the method would prove more valuable than complement-fixation tests and the estimation of antibody titres.

Dr. W. RITCHIE RUSSELL (England) discussed systemic treatment in the acute stage. Physical rest was still their strongest weapon, and sedation was a necessary corollary. However, preparation for respiratory failure, either because the centre was drugged or because of obstruction, was then doubly necessary. Eighty per cent. could be treated at home in the acute stage, but the remaining 20% needed expert attention. Respiratory treatment centres, he thought, should be in general hospitals. Paralysed limbs should not be immobilized, but passive movements regularly performed. Frequent changes of posture were necessary.

Dr. J. WHITTENBERGER (U.S.A.) described the respiratory disturbances in poliomyelitis. Neurogenic disturbances might cause weakness or paralysis of the respiratory or swallowing muscles: furthermore, loss of central control might affect alveolar ventilation, rhythm, depth, and co-ordination. A positive pressure in the mouth or trachea, he continued, had the same effect on lung volume as a negative pressure from a tank respirator, but "secondary effects on pulmonary blood flow may have a slight effect on gas exchange." Dr. H. L. HODES (U.S.A.) was in favour of using a tank respirator early in diaphragmatic paralysis, especially in certain patients with sleep difficulties. Weaning was gradual, with the help of a cuirass or rocking bed. Inability to synchronize could often be overcome by electrophrenic respiration. In the bulbar, often panic-stricken, patients tracheotomy coupled with postural drainage and aspiration was the rule, and respirators played no part. Digitalis and vasodilators helped.

Professor H. LASSEN (Denmark) was invited at short notice to address the meeting. He gave the figures from the 1952 epidemic, which showed the value of tracheotomy with a cuffed tube and positive pressure.

In the afternoon these papers were discussed, and Dr. C.-G. ENGSTRÖM (Sweden) described his positive-pressure apparatus and reported good results with it.

Gamma Globulin and Immunity

The next day Dr. P. LÉPINE (France) opened a discussion on infection and immunity. There was no permanent reservoir but man, he said. He then reviewed epidemiological data on subjects such as the development of antibodies in the absence of an epidemic and the faecal excretion of virus as the only sign of an epidemic.

Dr. J. H. S. GEAR (South Africa) said neonates inherited antibodies from the mother which disappeared in from three

to six months. In primitive insanitary communities all three strains were common: 90% of children under 6 had immune bodies to type II, and most to types I and III; paralysis occurred almost exclusively in infants, and epidemics were unknown. On islands, whereas immunity was limited to one type, epidemics might occur. Sanitation reduced the chances of natural exposure and therefore also of natural immunity.

Dr. H. MUENCH (U.S.A.), a biostatistician, described the outcome of tests to evaluate passive immunity after children had been given gamma globulin or gelatin one to seven weeks before exposure. The 1952 tests indicated that gelatin might have been a cause of paralysis in the injected leg of some who had it. Nevertheless, by making adjustments (which he stated was contrary to his statistical conscience) the figures had shown a significant difference in favour of gamma globulin. In 1953 mass-injection tests produced no such favourable effects, according to the National Advisory Committee. But, if judged by the appearance of the expected shift of cases from younger to older persons, the gamma globulin did seem effective, and this was so in all the 13 mass-injection areas. He concluded that mass gamma globulin was of some value.

Dr. W. McD. HAMMON (U.S.A.), who was in clinical charge of the Pittsburg trials in 1951 and 1952 referred to above, said they were anxious to know whether gamma globulin injections interfered with the acquisition of immunity. Virus was isolated from 395 faecal specimens, and the virus was typed in 262, neutralization tests done in 1,006, and complement-fixation tests in 1,905. The results pointed to little interference with infection—that is, the exposed children became virus carriers in almost the same proportion as those not given gamma globulin.

Active Immunization

Dr. J. E. SALK (U.S.A.) described the basic steps in developing poliomyelitis vaccine. His vaccine was a formolized and therefore dead vaccine, whereas others looked to a live but weakened virus. The vaccine must contain all three known types. The vaccine was grown in tissue culture, attenuated with 1 : 4,000 formaldehyde, and its infectivity and antigenicity were tested. Infectivity fell much more quickly than antigenicity. After excluding the possibility of virus B infection (a disease in monkeys), tuberculosis, and the virus of lymphocytic choriomeningitis, 650,000 children were inoculated, with only the most trivial reactions in a small proportion. The intervals were 10–14 days between first and second, and 5–6 weeks between the second and third, inoculations. Antibody response was satisfactory: good for type II, though slightly less so for the others. "Booster" doses might cause some refractoriness. Much had still to be learnt, but it did appear that, by suitable manipulation of the dose of vaccine and of the intervals between inoculations, it should be possible with relatively few injections, properly spaced, to produce long-term immunity. Clinical trials were in progress, and the results would probably be available in March.

Dr. A. B. SABIN (U.S.A.) said that persons inoculated against yellow fever were safely and soundly protected although the vaccine was a live one. He described the search for a similar virus for poliomyelitis: naturally occurring modified viruses such as those causing minor illnesses in children, which had limited infectivity for monkeys, formed the basis of his researches. His results were promising.

Dr. JOHN ENDERS (U.S.A.) then presided at a panel discussion on tissue-culture technique. Although this is a highly technical subject it must be remembered that it was Dr. Enders's discoveries in this field that had led to the triumphant sequence of complement-fixation tests, vaccine preparation, diagnostic tests, and assays of virus.

Orthopaedic Treatment

On Thursday the orthopaedic surgeons and specialists in physical medicine discussed their problems. Professor C. COLONNA (U.S.A.) condemned early surgery. Fasciotomies and lengthening of tendons had proved their worth; muscle transplants needed very careful planning. Professor C. MARINO-ZUCO (Italy), the general chairman of the conference and professor of orthopaedics at Rome, described his operation for lengthening the shortened femur. In some cases he went so far as to advise arthrodesis of the shoulder.

Dr. ANNE BARRIÈRE-BORCHARD (France) stated that complete rest was needed in the acute stage and early convalescence, while Dr. H. J. FLAX (Puerto Rico) said the "physiatrist" should start work at the very onset if deformities were to be prevented. Dr. S. MEAD (U.S.A.) said no basic principles had changed since Roth enunciated them in 1884. He advocated early movements after the natural disease and after operations; he had never seen bad results after early movements. If patients had to get along without a muscle they must be told the truth early.

Concluding Sessions

On the last day Dr. A. M. M. PAYNE (W.H.O.) spoke of poliomyelitis as a world problem. He described the varying distribution, and showed that often a falling infant mortality rate coincided with a rise in attack rate from poliomyelitis, possibly owing to better notification. When the infant mortality fell to under 50, the risk of severe epidemics was much greater. The other speakers summarized special views. Dr. T. M. RIVERS (U.S.A.), discussing the epidemiology, said that person-to-person transfer seemed commoner than infection from water, the nose being of little significance compared with the pharynx and gut. Viraemia was most important, and transfer to the central nervous system from the blood was probable. The distinction between non-neuro- and neurotropic types was a matter for further research; great possibilities ensued if stable mutants could be isolated. All were eager to hear the results of the trials of the formolized vaccines. He concluded that it was unwise to regard gamma globulin as a practical public health measure.

Dr. G. FRONTALI (Italy) emphasized the necessity of adequate sleep and its bad effects if not secured. Dr. R. DEBRÉ (France), discussing the social aspects, said that fear must be allayed; excessive fear might overwhelm a community.

Dr. JOHN PAUL (U.S.A.), in summarizing the proceedings and attempting to look into the future, declared that the only safe prediction was that all would remember with great gratitude the wonderful hospitality of their cordial and genial hosts. The crying need was for a vaccine. But they must answer four questions: (1) Would immunizing agents prove harmful? They could reply that mass human experiments had shown exceptionally few troubles. (2) Was antibody a good index of protection? Only clinical trials could answer this. (3) Would antigen, dead or alive, produce the desired immunity? Again, clinical trials must give the answer. (4) How long would active immunity last? Research started now would show this in due course.

BRITISH ASSOCIATION

[FROM A SPECIAL CORRESPONDENT]

Some of the contributions to the annual meeting of the British Association, which was held in Oxford from September 1 to 8 under the presidency of Dr. E. D. ADRIAN, F.R.S., were summarized last week (p. 641). The following is a concluding report of the meeting.

Chromosomes and Genes

A full-day session on chromosomes and gene structure, held jointly by the Sections of Zoology and Botany, was opened with an account by Dr. E. J. AMBROSE (Institute of Cancer Research, London) of physical phenomena which might be correlated with the biological function of chromosomes. With the high resolution of the electron microscope fibres of diameter 200 Å (0.02 micron) running parallel to the length of the chromosomes had been observed in

several types of dried cells, including human cells. There was a suggestion of beading at intervals of 700 Å along the fibres. Dimensions of 700 Å by 200 Å were of the order of size of virus particles, and from these segments regular fibres resembling chromosome threads had been produced, dispersing and re-forming without loss of biological activity, and showing optical and elastic properties similar to chromosomes. The parallel fibres appeared to be held together by forces of an electrostatic nature, and chromosomes could be made to swell and contract reversibly in a direction at right angles to their length by changing salt concentration. Stable pairing of threads had been observed in living cells at separations of up to 8,000 Å. Along the length of the fibres, the process of chiasma formation during meiosis could be accounted for on the basis that a thousand or more variously shaped giant molecules were strung together by secondary forces.

Dr. J. CHAYEN (research worker, British Empire Cancer Campaign) began by summarizing the considerable body of evidence which points to deoxyribose nucleic acid (D.N.A.) as the chemical basis of the gene; for example, the association of a given set of chromosomes with a constant amount of D.N.A. But he considered that his own recent work (on the cells of root tips of the broad bean) made it unlikely that D.N.A.—though associated with the gene—was its prime substance. In these cells he had found migration of D.N.A. between cytoplasm and nucleus, and in his view the whole question of the localization of D.N.A. would need to be reinvestigated. The gene might be found to be something far more interesting than merely a sequence of nucleotides. Dr. J. M. THODAY (Sheffield University), who followed, stated that he would have liked an extra 24 hours to reconsider his own contribution, although this made only a single point which appeared definite. Comparison of data on the breakage of chromosomes by *x* rays and alpha particles with data obtained by Howard and Pelc on the synthesis of chromosomal nucleic acid using radioactively labelled sulphur and phosphorus indicated that such synthesis occurred at about the same part of the mitotic cycle as the chromosome reproduction.

Localization in the Cerebral Cortex

A symposium on localization in the cerebral cortex, held by the Section of Physiology, was introduced by Dr. ADRIAN. He distinguished as two possible approaches those which attributed the advantage of a large brain (1) to the facility which it offered for local specialization, and (2) to the large mass of undifferentiated tissue available for the service of whatever activity was proceeding, the former interpretation having been favoured strongly 50 years ago. As regards afferent signals, there was quite enough anatomical and electrical evidence to trace them up to the brain surface, but their further pathways were not known. Professor E. G. T. LIDDELL, F.R.S. (Oxford University), showed the existence of overlap between motor centres, and suggested that the concept of strict localization had owed something to draftsmen. Dr. F. P. GLEES (Oxford University) and Mr. J. COLE illustrated with a film experiments on sensori-motor skill in monkeys, which included the performance of acquired skilful acts, tests of grip-strength, dexterity, and discrimination, and the effects produced by removing one of the subdivisions of the motor cortex or by many small lesions. They concluded that the performance of an acquired skilful act is dependent on the motor area, but (from the study of recovery) that the mozaic-like conception of the cortex was no longer justified; reorganization of function was perhaps due to a wide overlap of both incoming and outgoing fibre tracts in motor and sensory cortices. Dr. J. A. V. BATES (Neurological Research Unit, National Hospital) suggested that the view that motor centres were localized in the cortex should be reconsidered, and that they should be thought of rather as localized in the spinal cord, where all possible information was represented, and where cortical, like sensory, signals were afferent.

The Thyroid and Evolution

The interest of seeing how far the functions of the endocrine glands may have changed in the course of evolution, in response to the changing stresses to which the vertebrates have been subjected, was given by Professor E. J. W. BARRINGTON (Nottingham University) as the justification for a contribution on the thyroid and evolution in the Section of Zoology. In fish, as in mammals, the pituitary and the thyroid were closely linked, as had been indicated by the production of goitres in fish immersed in solutions of thiourea or thiouracil, since these substances arrested the production of thyroid hormone and so of pituitary thyroid-stimulating hormone. But it had proved difficult so far to find any close correspondence in functions between the two groups. There was evidence, however, that in certain fish the thyroid was especially active at periods of crisis in the life-history—for example, at the time of migration of salmon smolt and of the silver eel. There was also seasonal variation in fish with less spectacular life-histories, and it had been suggested that the thyroid might be concerned with the activation of those centres which set off particular behaviour patterns, such as those associated with migration and reproduction. The importance of investigating such problems was not limited to intrinsic interest, but included the possibility that they might reveal fundamental properties of the thyroid which had become obscured in mammals by special adaptations.

Milk Ejection

The comparative physiology of suckling and milking was considered in a session held jointly by the Sections of Physiology and Agriculture. Professor H. D. KAY, F.R.S. (National Institute for Dairy Research, Reading), introducing, said that recent scientific knowledge of the physiological mechanisms underlying the liberation of milk had had important practical applications both in the dairy farm and in relation to efficient human lactation. Dr. B. A. CROSS (Cambridge University) recalled that emotional inhibition of the milk-ejection reflex was a well-known phenomenon in both departments. It occurred in rabbits when suckled under conditions involving forcible restraint. Two mechanisms were concerned. The more important was a central inhibition of reflex oxytocin release from the posterior pituitary gland. The other was a peripheral effect involving constriction of the mammary blood vessels, thus limiting access of oxytocin to the contractile elements responsible for milk ejection. The latter effect could be produced by electrical stimulation of the sympathetic centres of the hypothalamus, the splanchnic nerve supply to the adrenal glands, or the mammary sympathetic nerves, and also by injection of adrenaline or noradrenaline. A subsidiary milk-ejection mechanism, which was unaffected by anaesthesia or emotional disturbance, was a local contraction process induced by direct mechanical stimulation. This mechanism might assist by removing the small amount of milk which came when the posterior pituitary milk-ejection mechanism was prevented from functioning.

The Deaf in Society

The problem created by the bringing together of deaf children into special schools away from normal children was considered by Mr. P. GORMAN (Cambridge University) in a contribution to the Section of Psychology. Though many people might think that the rehabilitation undertaken by public and private agencies was sufficient, it had really only just begun. The few deaf people who had integrated successfully with hearing people had done so in ways not usually or easily accessible. Impartial and unemotional research must, he stated, be undertaken before the question whether deaf people can or should integrate into general society could be answered; and many of these problems were applicable to others possessed of mental or physical defects.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Medical Responsibility

SIR,—Surely the decision of the first Division of the Court of Sessions in Edinburgh on July 21, reported in the *Journal* of July 31 (p. 308), and your important and wholly admirable leading article under the above title in the same issue (p. 290) must have increased the deep uneasiness already existing throughout the profession. A legal position in regard to medical responsibility, arbitrary in itself and highly detrimental to good medicine, now appears to have been firmly established throughout the country by a series of English judgments in the last ten years and now confirmed for Scotland also. In the case of *Hillyer* v. *St. Bartholomew's Hospital* in 1909 it was ruled that the governors of the hospital were not liable for a burn by a hot-water bottle sustained in the operating theatre: and the new situation created by the provisions of the N.H.S. Act has to-day determined almost completely the turning of the legal attitude full circle from the classical and basic decision of that year. Lord Cooper has enunciated that the Act imposes an obligation on the State to *treat* the patient, the doctors being "the agents to whom the boards had delegated the performance of the duties imposed on the boards by statute," and the boards, therefore, wholly liable for any mishap held culpable.

So far only resident or whole-time professional staff (deemed permanent staff) have been included. But this is obviously a wholly arbitrary position, a delicate balance which cannot endure as a final solution. What will be the next clarifying legal decision? Is it to be the inclusion of the medical hierarchy under whom these officers are assigned duties? Lord Denning for his part thinks they should be so included.

Surely, Sir, the position is a precarious and grave one. Responsibility is being lifted from the doctor and placed on the State. Hitherto the State has been deemed to have discharged its public responsibility by imposing tests of competence upon aspirants to the ranks of the profession, with disciplinary safeguards. But now every crucial act or decision by the bedside, in the theatre, every line of treatment chosen after abstruse haematological, biochemical, or any other pathological investigation is logically to become a decision for which the State, rather than essentially the doctor, is to be responsible, this learned profession being just a group of employed technicians. One even tries to visualize the institution of a vast snooping super-inspectorate into every corner of practice, in other words a voyage into a fairyland, as seemingly the only response the State can attempt to the demands now threatening to be placed upon it by the current interpretation of the law as it stands, a position already seriously exacerbated by the effects of the Legal Aid Scheme. We have now reached a fully confirmed crisis in this matter, a crisis containing an immense fallacy and imperilling the doctor–patient relationship in favour of a State–patient relationship, and, I submit, urgently requiring consideration by the Council of the B.M.A. with the aim of securing an amendment of this section of the Act. What is good for the best practice of medicine is good for the public.—I am, etc.,

Newquay. F. A. ROPER.

Selection of Medical Students

SIR,—Dr. Maurice Davidson (*Journal*, September 4, p. 594) takes a poor view of the medical student of to-day which I, as a trainer of trainees, do not share. I am very impressed with the extent of the knowledge of the trainees who have passed through my hands, and the attention which has been paid to their medical education. I remember, when I was a student 25 years ago, a revered chief dwelt on the influence on medical literature of a knowledge of the dead languages: and one of Kai Lung's characters remarks that "a person of true refinement would have expressed much of that very differently, but nothing will ever make up for the lack of a classical education." But surely what we are really concerned about is the production of good practitioners of physic in all its branches, and the philosophy of the Hellenic sages is still a living force in living men who have never studied the classics. It is the influence and spirit of the teachers which will mould the thought; what they teach is of less importance. Just as a school is fired down to the smallest boy by an enlightened headmaster, so a medical school and its traditions are shaped by the consultant staff headed, as you have noted in another article, by the dean.

In the obituary notice of Sir James Spence (*Journal*, June 5, p. 1327) it was remarked that his resident appointment at Great Ormond Street "probably determined in some measure the pattern of his life, for it has been said that those who are privileged to work at this hospital are influenced by it for the rest of their lives." If the selection boards choose each year a crop of students who are of reasonable intelligence and personality and of good character, that is surely all they can do; there are really no other guides. Latent in each is that spark which if once kindled can alter him. "One of the great rewards of teaching is to see, not once but again and again, how one boy indistinguishable from the others in an average group will, stimulated by a single remark of the teacher or excited by exploring a new subject, suddenly begin to change. . . . Somehow, some happy change or providential effort has caused the energies of his mind to combine in a new, creative, synthesis."[1] It should, therefore, be the aim of the profession to improve itself by concentrating on those who will inevitably influence the coming generations. In the teaching hospitals, greater attention should be paid to the character of the candidates for consultant posts. The Health Service, with its relative absence of incentives, is being an acid test of the sense of vocation of the profession as a whole; I am not sure that we are standing up to it very well in the eyes of the public, and, if that be so, we must do better in the future. I would here add a plea for the scheme for trainee general practitioners. I am sure that the intention which lies behind it is right; I am equally certain that it has very often been misapplied and that a wonderful chance is slipping away. There could be no better training for a young practitioner in his most impressionable phase than to come for a year under the influence of a sound man of mature experience and of high standing and character. There are not many such, but it should be a great honour and a great stimulus to be a trainer of trainees. The recent B.M.A. memorandum on the subject I found inadequate and disappointing and likely to be of little use.

This must always be an imperfect world, and none of us can achieve what he would desire to do or to be. I may not do them credit, but I have never forgotten the kindness and interest of some of my chiefs in my years in hospital after qualification, and I wish that I had been able to sit at the feet of Girdlestone and Hugh Cairns in Oxford. But this I do know: that if my son desires to follow me it will be my aim to place him under the influence of those who are of mind like to these in the hope that he will one day be inspired by his teachers and not merely taught by them, so that he could be worthy of the very great trust which might, one day, be his. We hear much about the scientific training of medical students, the need for education in the humanities, and so on. It would be better if we of the active generation were to turn our thoughts to what we should do, to what we are, and to what we are not.—I am, etc.,

Shipton-under-Wychwood, Oxon. GORDON SCOTT.

REFERENCE
[1] *The Mind of Man*, 1954. Oxford Univ. Press, London.

SIR,—If Sir Francis Drake wished to circumnavigate the globe to-day he would not be allowed to do so. He would be stopped because he had no passport, and arrested for taking money out of the country. If by any chance he managed to elude the port authorities he would certainly be detained on Ellis Island because he had not been vaccinated.

After reading the articles on selection of medical students in your recent number it appears to be equally difficult to

enter a medical school to-day. Unless you can satisfy a selection committee that you are under 30 (in heaven's name, why ?) and are an ectomorphic mesomorph (whatever that is) with an I.Q. about equal to that of Leonardo da Vinci and/or Einstein, you are promptly turned down. Is there no room in the medical profession to-day for the man who simply wants to be a doctor ? Incidentally, who selects the selection boards ? The only board I can think of likely to assess accurately the future life, career, and suitability of a candidate is the following—the Archangel Gabriel (chairman), Old Moore, Nostradamus, and Mother Shipton (members). I can see William Harvey being turned down for his crack-brained idea that the blood went round and round. Ronald Ross would undoubtedly have failed for wasting time dissecting mosquitoes' stomachs.—I am, etc.,

Leeds. W. STANLEY SYKES.

Tetanus

SIR,—The three reports in the *Journal* of August 21 (pp. 442–5) of cases of tetanus, in all of which some form of muscle relaxant was used, show that there is still confusion of thought about a method which, logically applied, promises to revolutionize the treatment of this disease. The fundamental points of this method are (1) to protect the lungs, by *early* tracheotomy, from contamination by secretions which the disorganized larynx can no longer exclude; (2) so to reduce the heightened tone of skeletal muscle that convulsions are prevented; (3) to maintain adequate respiration; and (4) to avoid drugs which depress the central nervous system.

Respiratory infection is the most important cause of death from tetanus. Persistent bronchial secretions and inhaled pharyngeal contents not only predispose to this infection, but also produce sensory stimuli which aggravate the muscular hypertonia. Tracheotomy protects the lungs and allows bronchial toilet to be performed with comparatively little disturbance. It is a characteristic of the disease that the degree of hypertonia varies unpredictably from minute to minute. The dose of muscle relaxant required to oppose it should be varied in conformity. The required dose will at times be sufficient to paralyse respiration, which must then be maintained artificially. This is true whatever muscle relaxant is used; but only a short-acting drug, such as succinylcholine, can meet the changing demand with sufficient rapidity to prevent overdosage. It is true that when artificial respiration—either manual or mechanical—is properly managed, overdosage probably does little harm, but it is obviously right in principle to relate the dose as closely as possible to the patient's needs.

Tetanus toxin attacks the basal ganglia : so do centrally acting depressants such as the opiates, the barbiturates, and paraldehyde. In spite of this disadvantage, these drugs were the only means of preventing convulsions before the advent of the muscle relaxants. Now that convulsions can be prevented by peripheral blocking, the centrally acting poisons are no longer needed. The tetanic patient, twisted into spasms by the toxin, is transformed by the logical use of the muscle relaxants into a flaccid patient with a paralysed larynx. The work of Lassen[1] and of Ibsen,[2] in the epidemic of poliomyelitis in Copenhagen in 1952, has taught us the correct treatment of the flaccid patient with a paralysed larynx. Let us be logical and diligent in our application of it.—I am, etc.,

Bristol. RONALD WOOLMER.

REFERENCES

1 *Lancet*, 1953, 1, 37.
2 *Proc. roy. Soc. Med.*, 1954, 47, 72.

Smoking and Lung Cancer

SIR,—Professor Sidney Russ (*Journal*, September 4, p. 578) asks how it is that cigarette smoking is thought to be responsible for the majority of deaths from lung cancer when people in the U.S.A., who smoke about 30% more cigarettes than we do, show a death rate from lung cancer less than half that of ours. I suggest that the reason is a difference in smoking habits. In the U.S.A. cigarettes are cheap. Many people discard cigarettes half smoked, while few smoke them to the bitter, bitter end as we do. In Britain cigarettes are dear, and one constantly sees fingers, not merely nicotine-stained, but blackened and burned. They are keratinized, too, and our hardened smokers extinguish what little remains, not under their heels, but between their fingers. We smoke, I suggest, relatively more of each cigarette we buy.

The tarry components of cigarette smoke, which may well contain the carcinogenic agents, condense partially in the bitter end referred to. As we smoke our gasper to the last gasp, these products go up in smoke again, and I suggest that we absorb a high concentration of carcinogens from our fag-ends. I guess that we inhale cigarette smoke more than the Americans do, for the same economic reasons, but I omitted to make actual observations of this when I was in the States. I declare that I have no personal interest in this matter—I smoke, I inhale, and my fingers are nicotine-stained. They are not blackened or burned only because I smoke filter tips in the hope of postponing lung cancer for an extra five years.—I am, etc.,

Murthly, Perthshire. HARRY STALKER.

SIR,—In regard to the medical memorandum by Professor Sidney Russ (*Journal*, September 4, p. 578), I doubt whether his statement that the people of the U.S.A. are the largest per person cigarette-smoking people in the world is correct. A recent visit to the United States convinced me that the sale of cigarettes is no indication for the amount of cigarettes actually smoked. A visit to restaurants or any other public place clearly demonstrates that Americans dispose of their cigarettes already after the first quarter has been consumed. This is an unusual sight when one comes from a country where tobacco is so expensive and every cigarette is carefully consumed. Public transport in the U.S.A. does not allow smoking; every day thousands of cigarettes just lit are being disposed of by people who enter the New York subway. Due to extensive touring of the United States I am convinced that the American habit of only partial consumption of cigarettes is an important factor in the relationship of lung cancer and cigarette smoking.—I am, etc.,

Oxford PAUL GLEES.

Obstetric Anaesthesia

SIR,—Perhaps the most surprising thing about this controversy is the almost total silence, so far, of the protagonists of the lithotomy position. Whether it is, as seems probable, that their case is so vulnerable, or whether it is that, ensconced behind the entrenchments of the lithotomy supports, they have developed a sense of immunity, it is difficult to say, but if they would lift their gaze beyond the narrow confines of those supports and view the patient as a whole they would, now and then perhaps, be constrained to share in some of the anxieties of the anaesthetist.

The trouble with those who teach the lithotomy position is that they fail to differentiate between the gynaecological patient, who is almost invariably properly prepared for anaesthesia, and the obstetric patient undergoing forceps delivery, who is seldom so prepared. The deplorable consequences of this have been made abundantly clear, and it cannot reasonably be denied after the series of deaths from aspiration of vomit, so courageously reported by Professor T. N. A. Jeffcoate (*Journal*, October 31, 1953, p. 951), Dr. R. B. Parker (*Journal*, July 10, p. 65), and others, that the lithotomy position carries with it a most serious risk to the patient in forceps delivery. Can anyone, on the other hand, produce records of a series of fatalities or even of one single fatality from this cause when the patient has been delivered in the lateral position, which at least immeasurably reduces, and probably entirely eliminates, this risk ? That some of the anaesthetists are acutely aware of the potential dangers of the lithotomy position in obstetrics is shown very clearly by the significant contributions from Drs. J. McAuley (*Journal*, July 24, p. 244) and R. G. Apthorpe (*Journal*, August 28, p. 536).

If, in spite of the fact that the lateral position offers a completely satisfactory solution, the lithotomy position is still regarded as sacrosanct, then indeed regional or local analgesia might well be used as a routine, but, as Mr. W. G. Mills remarks (*Journal*, August 21, p. 468), it does not appear to arouse any enthusiasm. In fact it is very probable that, had the obstetricians been faithful to the lateral position, little or nothing would have been heard of regional analgesia for delivery. Incidentally, Mr. Mills's assertion that it is remarkably difficult to anaesthetize a patient in the true Sims position surprises me, as I have always found it to be exceedingly easy, provided one is content with a simple mask and drop bottle. If this is combined with what Dr. Bryan Williams (*Journal*, December 26, 1953, p. 1433) realistically describes as "the supreme safety of open ether," one has all the conditions for safe delivery.

Perhaps one further reference to Dr. R. B. Parker's excellent article might be allowed as an afterthought to my letter in the *Journal* of July 31 (p. 299). When he describes somewhat euphemistically certain "preventive" measures for dealing with vomiting, they are for the most part merely expedients for dealing with a catastrophe which ought not to occur and which almost certainly never would occur to a patient delivered in the lateral position. Surely it is better to allow the inexorable law of gravity to operate in the patient's favour than to court disaster by defying it. It can hardly be denied that the accumulated evidence against the lithotomy position for forceps delivery constitutes a formidable indictment, and it is indeed difficult to see how those responsible for the teaching of obstetrics can continue to regard the present position with equanimity.—I am, etc.,

London, N.W.7. A. H. MORLEY.

SIR,—May I be allowed to comment on some points raised in your correspondence columns following my article on the aspiration of vomit in obstetric anaesthesia (*Journal*, July 10, p. 65)? First, I thought it pertinent and proper in such a paper to discuss the merits of the different methods of anaesthesia which are available to obstetrician and anaesthetist for operative delivery, but from lack of competence to do so I stopped short of discussing the pros and cons of different techniques of inhalational anaesthesia. I now realize that in doing so, and thereby omitting references to the writings of anaesthetists in this field, I may have been guilty of implying that such work was lacking or that I was unaware of it. May I therefore repair this omission by paying tribute to the classical paper by Morton and Wylie[1] and the recently published article by O'Mullane,[2] both of which have provided me with much food for thought? In the former there are specific recommendations for the *inexpert* anaesthetist who is to give an inhalational anaesthetic to a patient whose stomach is certainly or very probably not empty (a group which includes patients in labour).

Their main points, which I should like to summarize, bear repetition. (1) Make every effort to empty the stomach through a Ryle's or 12-bore oesophageal tube, and leave the tube *in situ*. (2) Use nitrous oxide, oxygen, and ether. (3) As soon as possible replace the Ryle's or 12-bore tube with a 24-bore oesophageal tube and maintain suction throughout the operation. (A cuffed endotracheal tube is advocated for the less experienced.) Masks designed to allow this to be done have been described by Morton and by Clutton Brock.[3] I note that Dr. E. Godwin (*Journal*, July 31, p. 299) after examining the alternatives comes reluctantly to the same conclusion as Morton and Wylie—namely, that the stomach *must* be emptied before an inhalational anaesthetic is commenced in these circumstances.

When the above recommendations are followed, trouble from aspiration should not arise, and our distaste for "the stomach tube," voiced by Mr. W. G. Mills (*Journal*, August 21, p. 468), should not blind us to the fact that it offers us the only assurance of safety. Indeed, I doubt if any modern technique which would avoid the preliminary emptying of the stomach could claim equal safety, even in the hands of the most expert; especially so if induction with thiopentone has to be modified in the interests of a premature or distressed foetus. (See contributions by Wylie and Morton,[1] O'Mullane,[2] and P. Hex Venn.[4]) If I am wrong in supposing this I should be very glad to hear it, as I regard the stomach tube with mixed feelings; and if it would assist the anaesthetist in evolving a safe alternative I should gladly press for the wider use of a proper (tilting) operating-table for all deliveries under general anaesthesia. For myself, when undertaking a forceps delivery in hospital I seek to use local or pudendal block analgesia whenever possible. When I feel that inhalational anaesthesia is called for I find a contentment in knowing that the stomach contents have been aspirated, which outweighs the distaste I have for the procedure. At the same time I continue to be interested in the results obtained by those advocating spinal and caudal analgesia, though I am not yet converted to their use.

Under this regime in a properly equipped hospital I believe that no additional safety will be conferred by the use of the lateral position as advocated by Dr. A. H. Morley (*Journal*, July 31, p. 299). Mr. Mills has pointed out its disadvantages, and most obstetricians would, I think, prefer to continue to use the lithotomy position for routine assisted delivery in hospital. I am not quite certain, too, that serious aspiration of vomit could not happen in the lateral position, though undoubtedly the risk of its occurrence would be diminished. In domiciliary practice, however, there seems much to be said for Dr. Morley's suggestion—i.e., where general anaesthesia is indicated. On the other hand, if we accept the limitations for domiciliary midwifery proposed by Jeffcoate and Jameson and Handfield-Jones,[5] then only those deliveries which can be undertaken under local or regional block will be done in the home. Therefore, in reply to Dr. A. Stephen (*Journal*, August 21, p. 468), I would certainly recommend him to become familiar with the use of lignocaine, as suggested in the last paragraph of Mr. Mills's letter. It would certainly relieve him of the anxiety he feels concerning chloroform. However, if, in exceptional circumstances, a general anaesthetic is required in the home, I cannot believe that there could be serious objection to the use of chloroform by someone familiar with its dangers; and if I were the operator concerned I should be prepared to attempt to conduct the delivery with the patient in the lateral position.—I am, etc.,

Birmingham, 15. R. B. PARKER.

REFERENCES

1. *Anaesthesia*, 1951, **6**, 190.
2. *Lancet*, 1954, **1**, 1209.
3. *Brit. J. Anaesth.*, 1953, **25**, 387.
4. *Lancet*, 1954, **1**, 1295.
5. *British Medical Journal*, 1953, **2**, 951.
6. *Lancet*, 1954, **1**, 665.

Assessment of Mental Defectives

SIR,—It is possible to seek too much in analysing the distribution of types in a single mental deficiency hospital or even in several in a homogeneous area. A hospital's population is not so much dependent on its own policy or a reflection of the population of its catchment area as it is a result of the social conditions of that area, and depends on the policy and opinions of the administrators and others in it. When I was starting Cell Barnes Colony, a wise adviser told me that hospitals in different parts of the country tended to get types of patients in different proportions, and I found this to be true. One very rural county, for instance, sent in feeble-minded girls only if they had illegitimate children. The others could manage in their local community. Time, alas, is a factor and produces changes in the grouping, as 20 years in one hospital showed. At one period we had many small children and many low grades—I no longer have access to the figures—then the children grew older and the low grades decreased and all the proportions were altered.

After the recent war the need was for the urgent admission of infants and toddlers, and, to a lesser extent, of low-grade adults. At the same time the criterion for admission was the urgency of need in the home, and patient situation. Patients who lacked the element of extreme distress had to remain on the waiting-list. It is possible that if O'Connor and Tizard,[1] McCoull and Slupinski,[2] or Millman[3] should repeat their analyses in ten years' time they may find quite different proportions from those they have published recently. On the value of the "psychometric assessment,"

especially in the socially inadequate group of the feeble-minded, I agree very strongly with Millman.[3] This assessment tells us something that is useful, but a defective is not defined as a person who produces a score below some chosen value when exposed to a series of tests of selected mental qualities ("a part of the whole"). He is still defined as one who needs help because of social or educational inadequacy. It is as a whole person in an environment that we have to judge his qualities and his needs.—I am, etc.,

London, S.W.19. NOEL H. M. BURKE.

REFERENCES

1 *British Medical Journal*, 1954, 1, 16.
2 Ibid., 1954, 2, 341.
3 Ibid., 1954, 1, 214.

Danger of Surf-bathing

SIR,—With reference to the letter by Dr. Michael Ash (*Journal*, September 4, p. 595) entitled "Danger of Surf-bathing," the Australian expert referred to is undoubtedly thinking of the one or two places on our south-west coast where surf is to be found, and it would seem that they have adequate life-lines in case of accidents. Dr. Ash does not appear to be aware of the fact that this Society caters very fully for the safety of bathers at practically all our seaside resorts by having its voluntary life guard clubs, life guard corps, and individual life guards in action equipped with a life-line, float, and harness. This equipment has been used for a number of years with the very greatest success, and many lives have been saved.

If Dr. Ash would like to have full details I shall be delighted to be able to assure him that, so far as it is humanly possible, swimmers and bathers are protected by representatives of the Royal Life Saving Society.—I am, etc.,

London, W.1. ALWYN E. BISCOE,
Chief Secretary,
The Royal Life Saving Society.

Cytodiagnosis of Bronchial Carcinoma

SIR,—I would like to support the remarks of Dr. F. Hampson (*Journal*, June 26, p. 1495) concerning the validity of cytological diagnosis in bronchial carcinoma. I also started the examination of sputum and bronchial washings in 1952, and have now come to regard it as a straightforward and reliable procedure. In the fifteen months ending in March, 1954, I examined 627 specimens from 299 cases, and gave a positive diagnosis in 52 cases. A careful follow-up study by the usual diagnostic methods has shown a total of 64 cases of proven bronchial carcinoma in the group, of whom, therefore, 81.2% showed recognizable malignant cells in sputum or bronchial washings. The cytologically positive group included 14 cases in whom, at bronchoscopy, biopsy was negative or not attempted.

These figures suggest that cytological examination in cases of bronchial carcinoma has a reasonable order of accuracy, at least as high as that usually given for the recovery of *M. tuberculosis* from cases of pulmonary tuberculosis by all bacteriological methods; that it is demonstrably superior to bronchial biopsy in securing a histological diagnosis; and that the hazard of false positives is extremely small. The views expressed by Dr. Raymond Whitehead (*Journal*, May 29, p. 1254) are in sharp contrast to those of many American and English pathologists, and to my own experience. Cytological examination of sputum is a simple and cheap procedure, when compared with bronchial biopsy. It can be repeated at frequent intervals without distress to the patient. In New Zealand, and no doubt elsewhere, it has the advantage of enabling specimens to be sent from smaller hospitals where there are no regular facilities for bronchoscopy. In those hospitals where cytological examination is introduced the results will quickly convince clinicians of its value. It would be most unfortunate if Dr. Whitehead's personal views should influence clinicians and pathologists against the establishment of such a diagnostic service.—I am, etc.,

Auckland, N.Z. STEPHEN WILLIAMS.

Genetic Patterns in Retinoblastoma

SIR,—Dr. L. I. Gardner (*Journal*, September 4, p. 591) suggests that in the interpretation of the inheritance of retinoblastoma a cytologically observed change in the X-chromosome of *Drosophila* showing bar mutation might give the answer as readily as the principles derived from peas by Mendel. No one who knows the immense elucidation of problems in human genetics that has come from the application of cytologically observed changes can possibly quarrel with any such suggestion. It may, however, be questioned whether there is any need to call in this particular cytological observation on the chromosome in the specific case of retinoblastoma, where the available evidence is all in favour of a simple explanation involving a single dominant gene.

It is accepted as proved that: (1) most retinoblastoma cases are "sporadic" and represent mutations; (2) where sibships are affected, a dominant pattern is not uncommon; (3) where no obvious dominance can be established two possibilities arise, one being that spontaneous cure of a retinoblastoma had occurred in one of the parents, and the other that the affection is not always expressed—that is, is "irregularly dominant." The first of these assumptions is an established, even if rare, clinical occurrence, and the second is likewise well established, for human genetics is full of examples of "irregular" dominance in monofactorial inheritance. "Irregular dominance" is hardly a somewhat rhetorical status, and there is certainly no evidence that retinoblastoma "'appears' and 'disappears'" in some families.

What is needed in the elucidation of the genetics of retinoblastoma is fuller data. In particular, information is required on the children of such retinoblastoma patients as have survived and produced progeny. Only one such systematic record is available, that by A. B. Reese,[1] who found that, of eight children born to five survivors of retinoblastoma who could be traced, seven were affected—a finding consistent with dominant inheritance, even if the incidence in this small number is higher than expected. Further information of this type is needed, and I should be grateful to any of your readers who could let me have details of the progeny of such retinoblastoma survivors as they have under their care. The birth of normal children is, of course, as important in such records as the birth of affected children; records of stillbirths are also important, for the gene for retinoblastoma might well prove lethal under certain conditions. Such information is not readily available at eye hospitals, and it is the general practitioner who can most easily obtain it. I would indeed be most grateful for help in collecting these data.—I am, etc.,

Ophthalmological Research Department,
Royal College of Surgeons,
London, W.C.2. ARNOLD SORSBY.

REFERENCE

1 *Arch. Ophthal. (Chicago)*, 1949, 42, 119.

Cyanacetic Acid Hydrazide

SIR,—All will surely deplore the indiscriminate use of a new drug before its value has been established both in the laboratory and by controlled clinical trials. Timely, therefore, is the letter from Dr. Margaret Barnett and her colleagues (*Journal*, July 31, p. 301), provided that this is interpreted purely at its face value. It would be a great pity if it should have the effect of dissuading those of us who are fortunate in having adequate facilities from carrying out clinical trials on this new hydrazide.

It appears to me that what Dr. Barnett and her colleagues are in effect saying is, first, that cyanacetic acid hydrazide ("reazide") is less active against tubercle bacilli than isonicotinic acid hydrazide, and, secondly, that tubercle bacilli which have become resistant to isonicotinic acid hydrazide are also resistant to cyanacetic acid hydrazide and *vice versa*. If their experiments are substantiated—they admit that these are as yet incomplete and are based upon work in various experimental animals and *in vitro*—then the scope of this new drug is clearly limited. It is to be noted,

however, that their findings are not entirely in accordance with those recently published and referred to in their letter by certain Swiss workers. The results of clinical trials, which I understand are at present in progress under the auspices of the Medical Research Council, will be awaited with interest, but even if these trials confirm Dr. Barnett's forebodings, cyanacetic acid hydrazide may well have a useful place, as indicated in the following case which I briefly report.

I recently had under my care a 52-year-old woman who tolerated perfectly several months' treatment with streptomycin and P.A.S. As soon as the streptomycin was substituted by isonicotinic acid hydrazide, she developed a rise of temperature and a gastro-intestinal upset. This ceased as soon as she was taken off isonicotinic acid hydrazide and recurred as soon as she was put back on that drug. When, however, continuing the P.A.S., I put her on to cyanacetic acid hydrazide, she was able to take this substance without any trouble at all. I did not treat her with cyanacetic acid hydrazide for sufficient time to evaluate its clinical effect, and in any case, of course, it would be ridiculous to draw conclusions from one case.

Intolerance to isonicotinic acid hydrazide (in doses of 4 to 8 mg./kg.) is, in my experience, exceptional. Furthermore, clinical trials in Switzerland[1] have shown that a certain amount of unpleasant symptoms may also be provoked by cyanacetic acid hydrazide. However, I suggest that those chest physicians who encounter patients unable to tolerate the older hydrazide might with profit try the effect of the newer one. And, of course, no chest physician would consider, in the present state of our knowledge, giving any hydrazide without either P.A.S. or streptomycin —I am, etc.,

Dartford, Kent. M. O. J. GIBSON.

REFERENCE

Scheu, H. (1954). *Schweiz Z. Tuberk.*, **11**, 77

SIR,—Dr. Margaret Barnett and her colleagues (*Journal*, July 31, p. 301) have stated that isoniazid-resistant strains of tubercle bacilli usually show increased resistance to cyanacetic acid hydrazide (C.A.H. or "reazide"). Our preliminary *in vitro* results with cultures of *Myco. tuberculosis* derived from patients, none of whom had had C.A.H., confirm this statement. The isoniazid sensitivity tests were carried out in Dubos and Davis' liquid medium[1] on the first set of cultures, and Löwenstein-Jensen medium on the second set. The C.A.H. sensitivity tests were all done in the liquid medium owing to the relative inactivity of the drug in solid medium. The strains were considered to be drug-resistant by the liquid medium tests if the minimum inhibitory concentration was at least eight times that of the standard H37Rv strain (which was inhibited by 0.03 μg. of isoniazid and by 2–8 μg. C.A.H. per ml. in the present tests). On the solid medium we regarded growth of 20 colonies or more in 1 μg./ml. or above as indicating resistance.

Sensitivity Tests	No. of Cultures	Isoniazid Sensitive C.A.H. Sensitive	Isoniazid Resistant C.A.H. Sensitive	Isoniazid Resistant C.A.H. Resistant
Isoniazid and C.A.H. in liquid medium ..	38	19	6	13
Isoniazid in solid and C.A.H. in liquid medium ..	27	15	7	5

The results are shown in the table. Of the 38 cultures tested for resistance to the two drugs in liquid medium, 19 were sensitive to both isoniazid and C.A.H., 6 were resistant to isoniazid but sensitive to C.A.H., and 13 were resistant to both. When the isoniazid sensitivity tests were done on solid medium, but the C.A.H. tests in liquid medium as before, 15 of 27 cultures were sensitive to both isoniazid and C.A.H., 7 were resistant to isoniazid but sensitive to C.A.H., and 5 were resistant to both drugs. There is, therefore, some indication that isoniazid-resistant tubercle bacilli are frequently resistant to cyanacetic acid hydrazide, though the clinical implications of these *in vitro* tests have yet to be assessed. It is probable that, as with any other anti-tuberculous drug, cyanacetic acid hydrazide should not be used alone. It should only be given to patients after careful consideration, bearing the above findings in mind.—We are, etc.,

SHEILA M. STEWART.
Edinburgh A. T. WALLACE.

REFERENCE

[1] *J. exp. Med.*, 1946, **83**, 409.

Creating Neurotics

SIR,—Talk of placebos brings to mind the huge number of neurotics to-day, and makes us ponder—is there *too much* doctoring to-day? Do too many people seek the services of the doctor as pilot when they could captain their own ship? Do too many people seek medical advice for trifles or for social problems—for problems of the soul—when, with a stronger faith, they would turn to minister or priest?

Further, there is no doubt that many neurotics are made by the foolish remarks of ill-advised if well-meaning acquaintances, and also, I fear, by over-anxious or over-conscientious doctors. I think it was Osler who said that doctors should never tell a patient the worst and rarely even tell the relatives. The physician should inspire hope and confidence and control his speech, expression, and manner, keeping his anxiety and worst fears to himself as much as possible.—I am, etc.,

Balfron, Stirlingshire. W. W. MACKINLAY.

Otitis and Recruitment

SIR,—I am puzzled by the number of young men I examine who have been rejected for the Forces by reason of ear conditions which appear trifling. Although medical boards may and do refer such persons to ear, nose, and throat specialists, I wonder if the latter always remember that Service conditions, both here and in many places abroad, differ little if at all from those found in civil life. An analysis of 10,000 causes of death in the records of insurance companies showed that only two of these were due to ear conditions. It would therefore seem unreasonable to reject doubtful cases because of the risk of death on Service or even, since many rejected lead active and healthy lives outside the Forces, from any fear of aggravation. It is always possible to keep them, if recruited, in the U.K.

Another aspect of this matter is that those rejected for trifling disabilities gain two years' civil experience and pay over those enlisted.—I am, etc.,

Hitchin. G. C. PETHER.

St. Luke's Day Service

SIR,—I should like, through the courtesy of your correspondence columns, to inform your readers of a special service for doctors which is to be held in October for the third year in succession in All Souls Church, Langham Place, W.1 (by Broadcasting House). The date this year is the day before St. Luke's Day, Sunday, October 17, and the service will be at 11 a.m. Situated near the centre of the medical world, All Souls, Langham Place, like St. Peter's, Vere Street, which is now united to it, has often been styled "the doctors' church." Many who attended the services of the last two years have encouraged us to arrange another this year, and I hope that doctors will welcome this opportunity of attending a service of prayer and dedication at the beginning of the academic year. The President of the Royal Society of Medicine and the President of the College of General Practitioners have kindly agreed to read the lessons. The preacher will again be the Rector.

Seats will be reserved for doctors (and members of their families) who apply for tickets in advance. Application (stating the number of tickets required) should be made to the church secretary, All Souls Vestry, Langham Place, W.1, by Thursday, October 14.—I am, etc.,

London, W.1. JOHN R. W. STOTT, Rector.

Obituary

Sir MAURICE HOLT, K.C.B., K.C.M.G., D.S.O. M.R.C.S.

The death of Major-General Sir Maurice Holt at Farnborough, Hampshire, on September 6 removes one of the oldest members of the Army Medical Services, which he joined in the year of Queen Victoria's golden jubilee. He was 92 years of age.

Maurice Percy Cue Holt was born on June 8, 1862, and was educated at King's College School and King's College Hospital, London, qualifying M.R.C.S. and L.S.A. in 1886. In the following year he began his distinguished career in the Army, a career marked by many honours and important appointments. In 1897 he was in medical charge of the expedition to North Zululand, work for which he received the thanks of the Colonial Office. He served throughout the South African War and was in the siege of Ladysmith, which lasted from the end of October, 1899, to the end of February, 1900. For his services in that war Holt was mentioned in dispatches, received the Queen's medal with three clasps, the King's medal with two clasps, and in 1902 he was awarded the D.S.O. Himself a surgeon specialist, he was responsible for the section of the official medical report on the South African War so far as it dealt with chest and neck surgery. After the war he served as a teacher of operative surgery at the Royal Army Medical College, Millbank, and in 1904 was nominated for the Taylor Prize in surgery.

Soon after the outbreak of the first world war in 1914—by which time he had attained the brevet rank of colonel—Holt became A.D.M.S. of a division, and later he was appointed director of medical services, with the temporary rank of major-general, to the Salonika Field Force—a post of great responsibility. For his war services Holt was appointed C.B. in 1915, being promoted to K.C.B. four years later, and K.C.M.G. in 1917, and was twice mentioned in dispatches. He also received a number of foreign decorations, including those of Grand Officer of the Star of Rumania, Grand Commander of the Order of the Redeemer of Greece, and Member of the Legion of Honour. He was also a Knight of Grace of the Order of St. John of Jerusalem. From 1919 to 1922, the year he retired from the A.M.S., he was Honorary Surgeon to the King, and earlier, while serving in India, he was appointed Honorary Surgeon to the Viceroy. He came out of retirement in 1928 to serve as colonel commandant, R.A.M.C., until 1932. He married Miss Sarah A. Busteed in 1887 and had one son and one daughter.

Holt excelled both as a surgeon and as an administrator, and these qualities brought him to real prominence in the first world war. Never one to shirk responsibility, not only did his surgical competence ensure his own promotion, but his flair for administration, allied with his technical skill as an operator, made him an excellent teacher of surgery to junior officers, whose advancement he encouraged. He also did much good work in regularizing the conduct and practice of surgery in the Army generally, and his ability in the dual capacity was of particular value in time of war.

Had Holt not decided upon the Army as a career it is likely that the Royal Navy would have had the benefit of his services, for he loved the sea. Much of his long period of retirement was spent aboard his yacht, *The Lady Wilmer*; from anchorages in the Beaulieu or Hamble rivers he would head out to sea, and there, exercising his skill as a mariner with the same competence he had shown throughout his Army career, he would be supremely happy.

A. BROWNFIELD FRY, C.B., C.I.E., D.S.O., M.D.

We record with regret the death on September 1 of Colonel A. Brownfield Fry, late of the Indian Medical Service, at the age of 81.

Arthur Brownfield Fry was born on May 29, 1873, the third son of the late Dr. J. W. Fry, of Wateringbury, Kent, and was educated at Eastbourne College and at the London Hospital, where he gained a medical scholarship and the Sutton Prize in Pathology in 1896. He qualified M.R.C.S., L.R.C.P. in 1896, and graduated M.B. at London University in 1898. Proceeding to the M.D. in 1909, he took the Cambridge D.T.M.&H. in 1910 and the D.P.H. four years later.

Fry had a distinguished career in the I.M.S., which he entered in 1899. He served in the Waziristan campaign of 1900–2, being mentioned in dispatches, and he took part in the Tibet Mission of 1903–4. In the first world war he served first in France and Belgium and later in Mesopotamia. During the war he was mentioned in dispatches three times, was awarded the D.S.O. in 1917, and became a Chevalier of the Legion of Honour in the same year. He was appointed C.I.E. in 1919 and C.B. on his retirement in 1930.

The Imperial Malaria Conference which met at Simla in 1909 recommended the appointment of a malaria officer for several provinces in India, and Fry was selected for the post of special deputy commissioner for malaria, Bengal. The reports of his investigations on the epidemiology of malaria in that province represent some of the earliest and best systematic work carried out in this field. He was the first professor of hygiene at Calcutta School of Tropical Medicine, a post which he held from 1922 to 1925. He investigated the epidemiology of cholera in India at the request of the Office International d'Hygiène Publique, and made a special study of the working and economics of slow and rapid filtration methods of water purification. From 1925 to 1930 he was assistant medical director of medical services in the Presidency district. He was appointed Honorary Surgeon to the King in 1927.

Fry was interested in all forms of sport, and was a particularly fine horseman. For several years after his retirement he revisited India each winter in order to indulge in his favourite pastime of polo. In this country much of his leisure time was devoted to shooting, fishing, and golf. He was unmarried.

ALFRED COX, O.B.E., M.A., LL.D., M.B.

Dr. L. A. PARRY writes: I must be one of the oldest, if not the actual oldest, B.M.A. friend of Alfred Cox. I had been selected as General Secretary of the B.M.A. Annual Meeting at Brighton in 1913. My first contact with him was directly after his appointment, and there was a good deal of advice and help I needed from him. I had it all along with the courtesy and kindness characteristic of him. I well remember when I was elected to the B.M.A. Council how he so tactfully helped to make me, a very junior member, feel at home in this august body. As a representative, as a member of many committees, and in many other capacities, I could always rely on his sound advice. It is a great source of satisfaction to me to be able to say we never had an unpleasant word. We may have differed and had view-

points not in agreement, but it was always in the most friendly way. I had not seen him very much since his retirement, but when we met it was always a pleasure to have a chat with him, and I like to think he felt the same. I lost a good comrade when Alfred Cox passed on. His friendship was to me a very real one.

Dr. KENNETH COWAN writes: You have published tributes to Dr. Alfred Cox from his old friends. May I, as a comparatively new friend, add an appreciation of a grand old man? Last December the Public Health Committee held an informal party to celebrate the completion of 50 years of work, and to it were invited past chairmen and secretaries. To our great delight Dr. Cox accepted our invitation. He met some of the old friends who had worked with him as well as the "youngsters," now members of the committee—and in a charming little speech he told us of his interest and of his work for the public health service members of the Association. I think I am correct in saying that this was Dr. Cox's last visit to B.M.A. House and one which I know he enjoyed. I am glad that we had this opportunity to pay a small tribute to him for all the work which he did for the public health service, and I know it will be a happy memory to all those who were present.

Miss M. H. ATKINS, secretary of the National Ophthalmic Treatment Board Association, writes: I had the honour and pleasure of working with Dr. Alfred Cox for only a few years, but I thought that you would be interested to know that one of Dr. Cox's last appointments was acting secretary to the National Ophthalmic Treatment Board during the years 1941 to 1946. Dr. Cox, as Medical Secretary of the B.M.A., was concerned in the formation of the National Ophthalmic Treatment Board in 1929 and welcomed the opportunity of renewing his association during the difficult war years, making the tiring weekly journey to the evacuated offices in Leicester during the first two years as a matter of course. Even after Dr. Cox retired, he continued to take a very great interest in the Board's work and latterly the work of the N.O.T.B. Association, making a point of calling at the office from time to time when on a visit to the B.M.A. Last year when I visited him in hospital he still showed keen interest in the future of the association. I shall greatly miss his delightful and characteristic Christmas letter, and his kindly but forthright and knowledgeable opinion on so many subjects.

Mr. C. E. MILNES BLUMER died in Staffordshire General Infirmary, where he was senior surgeon, on August 29, one day before his 56th birthday. Born in 1898, the son of the late Dr. Frederick Milnes Blumer, of Stafford, Charles Eric Milnes Blumer was educated at Marlborough College and at Edinburgh University. Towards the end of the first world war he served in the Army, first as a private in the Sherwood Foresters and later as an officer in the North Staffordshire Regiment. Returning to Edinburgh on demobilization, he graduated M.B., Ch.B. in 1923, and three years later became a Fellow of the Royal College of Surgeons of Edinburgh. After graduation he held house appointments at Staffordshire General Infirmary, the Royal Hospital, Wolverhampton, and the General Lying-in Hospital, Lambeth, before joining his father at Stafford, where he combined the work of his general practice, as his father had done, with many useful years as a surgeon at the Staffordshire General Infirmary, to the staff of which he was appointed in 1927. He gave up general practice in 1947 to become a consultant in obstetrics and gynaecology, always his main professional interest, and a year later, with the advent of the National Health Service, he was appointed consultant obstetrician to the Stafford group of hospitals. Mr. Milnes Blumer was a shy, undemonstrative, and modest man who nevertheless had a host of friends and no enemies in any walk of life. He published little, and took no part in clinical meetings or discussions, but in 1951 he was persuaded to be chairman of the North Staffordshire Division of the British Medical Association. He took a prominent part in establishing the Stafford branch of the British Legion, of which he had been president for many years. In the last war he was for a time commandant of the Stafford Home Guard. In May this year, fully aware that he had little time left, he characteristically returned to work and carried on uncomplainingly almost to the end with self-effacing deliberation. His wife died a year ago. He was a devoted father of a daughter and two sons, and the last happy event in his life was to witness the ceremony at which his elder son graduated in medicine in June this year.—J. MACD. H.

Dr. F. RUPERT SNELL, who was in general practice in the Trent Bridge district of Nottingham for many years, died on August 29 at Bournemouth, where he had been living in retirement. He was 74 years of age. Francis Rupert Snell was born on October 15, 1879, and studied medicine at Durham University and at St. Thomas's Hospital, graduating M.B., B.S. in 1905, and taking the M.R.C.S., L.R.C.P. in the following year. After graduation he held the appointment of assistant house-surgeon at the Nottingham General Hospital, and not long afterwards he settled in practice in the city, his work there being interrupted by service in the war as a captain in the R.A.M.C. He was in charge of an *x*-ray unit in the *Mauretania* for a time, and later served on the Somme and in military hospitals in this country. His ambition to become a medical missionary was denied him for health reasons, but he maintained an active and lively interest in many missionary hospitals and gave them valuable aid by starting in his own home the C.M.S. Hospitals Bandage Scheme. It was through his initiative and drive that the scheme spread widely and has resulted in half a million bandages being sent overseas. After his retirement from general practice in 1934 he, with Mrs. Snell, visited all the C.M.S. hospitals in East and West Africa. Subsequently he lived at Wimbledon, and then for some eight years at Burton Joyce, Nottinghamshire, before he moved to Bournemouth in the spring of this year. At Burton Joyce he was an honorary lay reader in the Southwell diocese and took a very active part in church affairs. When he was in practice his happy and friendly personality made him a very welcome visitor to the sick. A keen gardener—for he loved flowers as well as human beings—he was most generous in his gifts of plants and flowers, and was a fount of sound advice. He is survived by his widow, to whom our deep sympathy is extended.—J. LL. D.

Universities and Colleges

UNIVERSITY OF GLASGOW

On September 8 the degree of M.D., with commendation, was conferred *in absentia* by diploma upon J. A. McFadzean.

SOCIETY OF APOTHECARIES OF LONDON

The following candidates, having completed the final examination, have been granted the diploma of L.M.S.S.A.:

W. R. Peniston, N. W. Fogg, G. W. Carp, R. D. H. Kelly, C. G. Young, H. A. Williams, C. D. Chilvers, N. S. Halabi, R. G. Tarrant, B. W. Subhyah, B. C. Roughton, K. P. Walker, R. V. F. Williams, L. R. Jenkins, M. M. Adams, S. K. Young, T. H. Harries, B. R. Morgan, R. J. W. Adamson, P. F. Stebbing, M. H. Khatan, R. D. Lowe, A. Danillowicz, J. A. Maling, A. M. Lindsay, M. N. Khurshid, F. C. V. Brightman, J. Grey, A. J. Lacey, R. Young, H. Backer, L. W. Reeves, D. V. Burke, S. Jones, R. M. Stewart, N. W. Sargent, G. Codd, E. S. Price, S. H. Jamaldeen, W. P. Neville, E. R. Frohlick, B. S. H. Hsu, P. Stanesby, D. W. Griffith, M. R. G. Houri, A. R. Matthews, G. L. Goodwin, D. K. Brooks, Chan Ban, S. R. Hunt, A. M. Freeman.

J. Wessels has been awarded the diploma of Master of Midwifery.

The following candidates have been awarded the Diploma in Industrial Health:

S. M. Bieber, R. B. Body, J. Cameron, R. L. Luffingham, W. M. McCutcheon, P. C. Murray, F. W. Newby-Good, B. L. Shapiro, K. M. Williams, J. D. Stewart.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 28** (No. 34) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	4	0	4	0	1	22	1	4	1	
Dysentery	341	58	180	1		217	23	74	3	
Encephalitis, acute	1	0	0	0		4	0	0	0	
Enteric fever:										
Typhoid	1	0	0	1		3	1	1	0	
Paratyphoid	8	2	5 (B)	0		12	0	1 (B)	0	
Food-poisoning	148	8		0		415	24		1	
Infective enteritis or diarrhoea under 2 years				7	15				14	33
Measles*	1,699	81	96	26	114	2,730	50	43	75	75
Meningococcal infection	16	2	4	2		24	0	9	2	1
Ophthalmia neonatorum	38	0	7	0		32	0	5	0	
Pneumonia†	217	9	73	3	2	235	11	114	4	
Poliomyelitis, acute:										
Paralytic	54	2	14	4	2	181	16	15	8	11
Non-paralytic	25	5				116	18			
Puerperal fever§	240	35	11	1	2	12	0	10	0	1
Scarlet fever	349	24	71	9	18	690	40	107	19	28
Tuberculosis:										
Respiratory	653	92	117	13				109	12	
Non-respiratory	90	5	23	2				25	3	
Whooping-cough	2,038	92	188	11	57	3,864	349	430	55	48

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	2	0	2	7	1	2	0	0
Influenza	3	1	0	0	0	0	0	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		1	0				1	0		
Pneumonia	142	19	18	8	6	123	9	14	14	6
Poliomyelitis, acute	3	1			0	14	1			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	73	8	7	3	5	78	7	11	1	5
Non-respiratory		2	9	0	0		1	1	1	1
Whooping-cough	1	0	0	0	0	2	0	0	0	1
Deaths 0–1 year	193	18	25	8	16	193	15	24	6	10
Deaths (excluding stillbirths)	4,430	615	468	103	143	4,208	598	502	103	161
LIVE BIRTHS	7,390	1046	425	214	404	7,414	1153	872	202	336
STILLBIRTHS	163	21	26			185	20	28		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Infectious Diseases

The only changes of any size in the incidence of infectious diseases in England and Wales during the week ending August 28 were decreases of 556 for measles, from 2,255 to 1,699, and 49 for dysentery, from 390 to 341, and an increase of 96 for whooping-cough, from 1,942 to 2,038.

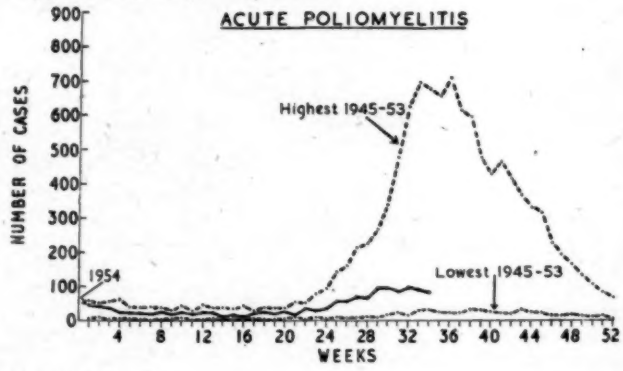
The 349 cases of scarlet fever notified were 30 below the number reported in the previous week and a record low number. 4 cases of diphtheria were notified—4 fewer than in the preceding week—and this also was a record low number. One case of diphtheria was reported from the following towns: Liverpool C.B., Eccles M.B., Plymouth C.B., Kingston-upon-Hull C.B. The decrease in the incidence of measles was mainly contributed by the northern section of the country; the largest declines were 110 in Yorkshire West Riding, from 216 to 106, 103 in Cheshire, from 213 to 110, and 101 in Durham, from 304 to 203. The largest variation in the trends of whooping-cough was a rise of 30 in Durham, from 93 to 123.

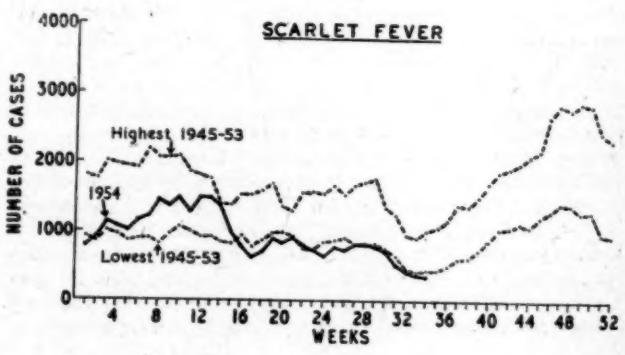
79 cases of acute poliomyelitis were reported. These were 1 fewer for paralytic and 9 fewer for non-paralytic cases than in the preceding week. The largest returns were London 7 (Woolwich 2), Northumberland 7 (Newcastle-upon-Tyne 5), Lancashire 5 (Liverpool C.B. 3), Cheshire 4 (Birkenhead C.B. 2), Durham 4 (Sunderland C.B. 2), Middlesex 4, and Yorkshire West Riding 4.

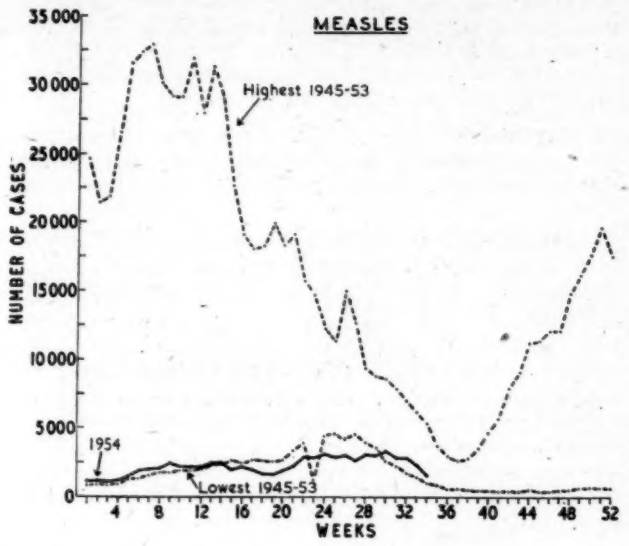
The chief feature of the returns of dysentery was an outbreak of 52 cases in Sussex, Uckfield R.D. The other large returns were London 58 (Wandsworth 19), Lancashire 47 (Swinton and Pendlebury M.B. 11), Yorkshire West Riding 44 (Leeds C.B. 11), Middlesex 23 (Ealing M.B. 11), and Staffordshire 15.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - -, the figures for 1954 thus ————. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Week Ending September 4

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 360, whooping-cough 1,988, diphtheria 11, measles 1,575, acute pneumonia 229, acute poliomyelitis 71, dysentery 317, paratyphoid fever 18, typhoid fever 6.

Medical News

St. Mary's Hospital Medical School Centenary.—The EARL OF VERULAM, President of St. Mary's Hospital Medical School, presided at a press conference on September 10 in anticipation of the centenary celebrations of the School, which have been fixed for November 30, when Queen Elizabeth the Queen Mother is expected to be present. Two exhibitions are to be held in connexion with the celebrations: one will illustrate research on penicillin and other antibiotics; the other will be a series of departmental exhibits by the staff and students. There will also be a special service at Paddington Parish Church. A public appeal will mark the centenary. It has two objects in view: first, to complete the quadrangle of the School buildings, for which something of the order of £450,000 is needed; secondly, to endow further research, and here no monetary target has been set. The annual dinner of the Medical School on September 25 will be made a centenary occasion, and a presentation will be made to Roger Bannister. Attention was also drawn to the publication of Sir Zachary Cope's book, published in connexion with the centenary, *The History of St. Mary's Hospital Medical School* (William Heinemann Ltd.). Sir ZACHARY COPE, whose personal recollections of St. Mary's go back over the whole of the second half of its existence, said that the purpose of his book was to record the advance of scientific medicine, as far as it related to St. Mary's, during the last hundred years.

1954 Medical Register.—The effect of the pre-registration year is apparent in the statistics for 1953 given at the beginning of the 1954 *Medical Register*. Over the last 10 years the average number of names added to the *Register* annually has been 2,897, but last year the total was only 507, of which 436 were Commonwealth, 63 from Ireland, and 7 foreign. In England there was one new registration, and in Scotland none. However, 1,817 provisional registrations were made. Taking registered and provisionally registered together, last year showed some falling off in new registrations in England compared with the exceptionally high levels of the previous three years, while in Scotland and Ireland new registrations were not much more than half the usual number. New Commonwealth registrations are now running at about double the pre-war figure. At the end of 1953 there remained 83,090 names on the *Register* and 1,813 on the *Provisional Register*, a rise, when taken together, of nearly 1,000 on the 1952 total.

Emergency Bed Service.—An unexpected trend recorded in the E.B.S. report for the year ended March 31, 1954, was the high number of applications last November and December for the admission of babies and very young children with respiratory disease. During that period about half of all respiratory cases dealt with by the service were in the 0–4 age group, compared with the usual proportion of 15–20%. Inquiries made by the Ministry of Health established that nearly every major city in England had suffered similarly. "There seems to be a general tendency," comments the report, "for 'epidemics' of respiratory disease to strike the very young before the middle-aged and elderly, though never has this phenomenon been so marked as in the past winter." During the year the London offices arranged the admission of 50,867 general acute cases (55,291 applications) and 9,495 infectious cases (9,720 applications). In addition there were 1,446 applications on behalf of chronic sick patients. The average time taken to admit a case last winter was 29 minutes, an improvement of one minute on the previous year. For each case it was necessary to approach an average of 2.8 hospitals, compared with 2.6 the year before.

International Confederation of Midwives.—Miss N. B. DEANE, President of the Royal College of Midwives, was elected President of the International Confederation of Midwives at the conclusion of the Confederation's congress in London last week. A well-defined constitution for the Confederation has resulted from this year's congress, with a council and executive committee, and a secretariat in London. Membership is open to any national organization of midwives whose certificate is recognized by its government. At present 22 countries belong, but there are indications that others, particularly from the East, are anxious to become eligible. The next congress will be in Stockholm in 1957.

British Journal of Haematology.—Blackwell Scientific Publications, Oxford, plan to start a new quarterly, the *British Journal of Haematology*, at the new year. The editor will be Dr. J. V. DACIE, with an editorial board consisting of Dr. SHEILA CALLENDER, Dr. D. A. G. GALTON, Dr. R. G. MACFARLANE, Dr. P. L. MOLLISON, Dr. A. E. MOURANT, Dr. R. R. RACE, F.R.S., and Dr. R. BODLEY SCOTT. An advisory board has also been appointed. In launching the new journal, the publishers point out that at present there is no British journal exclusively devoted to the subject of haematology. The *British Journal of Haematology* will publish papers on all aspects of haematology. Each issue will be about 96 pages, printed on art paper. The annual subscription is £2 10s. (post free); single copies 15s. each.

U.S. Troops and Influenza Vaccination.—According to a statement from the Surgeon-General's office in Washington, all American troops, wherever stationed, will be vaccinated against influenza this year. Vaccination is to be completed by November 15.

Family Planning Association.—A list of F.P.A. Voluntary Clinics in England, Wales, and Scotland may be obtained for 1s. (post free) from 64, Sloane Street, London, S.W.1. The list is revised quarterly. At some clinics premarital advice and advice on subfertility are given in addition to help with birth control.

COMING EVENTS

"The Child Through the Ages."—A new exhibition is now open at the Wellcome Historical Medical Museum (28, Portman Square, London, W.1) on the management of children and their diseases from the earliest times until the beginning of the present century. The exhibition includes a section on the care of the child among primitive races. Opening times: 10 a.m.–5 p.m. daily, including Saturdays.

Television.—A documentary programme, "Medical Officer of Health," will be televised from 9 to 10 p.m. on September 21. At 8.35 p.m. on September 20 JEANNE HEAL will introduce a half-hour programme on "Aids for the Handicapped"—a demonstration of appliances, arranged in association with the British Red Cross Society and King's College Hospital, London.

National Smoke Abatement Society.—21st Annual Conference at Scarborough, September 22–24.

William Blair-Bell Memorial Lecture.—Dr. THOMAS E. C. BARNS will lecture on "The Natural History of Pelvic Tuberculosis" in the Barnes Hall of the Royal Society of Medicine on September 24 at 5 p.m. Admission by ticket only, from the Secretary, Royal College of Obstetricians and Gynaecologists, 58, Queen Anne Street, London, W.1.

Vellore Reunion Meetings.—At the Caxton Hall, Westminster, S.W.1, on October 6. Chairmen: 3.30 p.m., Sir PHILIP MANSON-BAHR; 7 p.m., Dr. EDITH SUMMERSKILL. Speakers include Dr. HOWARD SOMERVELL and Dr. DONALD PATERSON.

Society of Apothecaries.—The Liverymen of the Worshipful Society of Apothecaries of London are summoned to appear at Guildhall on Wednesday, September 29, at 10.30 a.m. After a service at the Church of St. Margaret, Lothbury, they will return to Guildhall for the election of a Lord Mayor (12 noon).

Lloyd Roberts Lecture.—Dr. CHARLES SINGER will lecture before the Medical Society of London on "How Medicine Became Anatomical," at 5 p.m. on September 30.

International Federation of Medical Student Associations.—General Assembly in Rome, October 1 to 5. Details from Mr. JORGEN FALCK LARSEN, 12, Kristianagade, Copenhagen (see *Journal*, July 24, p. 238).

Film at B.M.A. House.—The Film Committee has arranged a showing of the film, "The Conjoined Twins of Kano" (recently acquired for the B.M.A. film library), at 8.30 p.m. on October 7. Any member of the Association will be welcome. Professor IAN AIRD will introduce the film.

Conference on District Nursing.—The Queen's Institute has arranged a conference on "Future Developments in District Nursing Services Associated with General Medical Practice" at the Royal Institution, Liverpool, on November 4 at 2.30 p.m. Speakers: Sir HENRY COHEN and Dr. J. L. BURN. Doctors will be welcome. Tickets from Queen's Institute of District Nursing, 57, Lower Belgrave Street, London, S.W.1 (not later than October 14).

"Tuberculosis and the Family Doctor."—Postgraduate course at Kingston Hospital and Chest Clinic, Kingston-on-Thames, October 23 and 24. Fee one guinea. Applications to Tuberculosis Educational Institute, Tavistock House North, Tavistock Square, London, W.C.1.

Wessex Rahere Club.—Autumn dinner at the Grand Spa Hotel, Clifton, Bristol, on October 23. Details from the hon. secretary, Mr. A. DAUNT BATEMAN, 11, The Circus, Bath.

London Medical Exhibition will be held on November 15 to 19 at the Royal Horticultural Hall, Westminster, S.W.1. Tickets from British and Colonial Druggist Ltd., 194, Bishopsgate, London, E.C.2.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Wednesday, September 22

MIDDLESEX COUNTY MEDICAL SOCIETY.—At Hillingdon Hospital, 4.30 p.m., Annual general meeting. Address by chairman, Mr. Howard G. Hanley: A Passing Glance at American Medicine.

Thursday, September 23

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.30 p.m., Presidential Address by Mr. Anthony Radcliffe: Evolutionary Changes in Otolaryngology

Friday, September 24

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, The University, Sheffield, 11 a.m., 332nd meeting.

APPOINTMENTS

JOEL, MARY F., M.B., Ch.B., Assistant Medical Officer of Health, Maternity and Child Welfare Department, Blackpool.

MATTHEWS, M. B., M.D., M.R.C.P., physician, and assistant physician to the cardiac department, Western General Hospital, Edinburgh.

RAMSAY, BARTHOLOMEW MACM., M.B., D.P.M., L.M., Assistant Inspector of Mental Hospitals, Department of Health, Dublin.

SZUMOWSKI, PIOTR, M.D., Clinician in Tuberculosis (S.H.M.O.), Royal Sea-bathing Hospital, Margate, Kent.

WILLIAMS, OWEN GLYNN, M.D., M.R.C.P., Director, Beck Laboratory, Swansea General and Eye Hospital, Swansea.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Appleton.—On August 11, 1954, at Boundary Park Hospital, Oldham, Lancs, to Pearl (formerly Osborn-Smith), wife of Mr. Norman Appleton, F.R.C.S., D.L.O., of 89, Queens Road, Oldham, a son—Graham Victor Norman.

MARRIAGES

Millard—Flenley.—On September 11, 1954, at St. Chad's, Poulton-le-Fylde, Lancs, Dr. John Leslie Millard to Dr. Margaret Kathleen Flenley.

DEATHS

Altmann.—On September 2, 1954, at Viège, Switzerland, the result of a car accident, Manfred Altmann, M.D., D.M.R.E., and his wife, Hannah, of 352, Finchley Road, London, N.W.

Annison.—On September 9, 1954, Richard William Annison, M.R.C.S., L.R.C.P., of 22, Powys Lane, Southgate, London, N., aged 68.

Atkinson.—On August 31, 1954, at Guy's Hospital, London, S.E., Cecil Hewitt Atkinson, *M.C.* (Two Bars), M.R.C.S., L.R.C.P., aged 60.

Back.—On September 1, 1954, at the Middlesex Hospital, London, W., Marjorie Back, M.D., D.P.H.

Barr.—On August 28, 1954, at Chesterfield, John Fulton Barr, M.B., C.M., of Hundall, Unstone, near Sheffield.

Bartlett.—On August 30, 1954, at his home, Brownie, Aldwick, Bognor Regis, Sussex, George Norton Bartlett, M.B., B.S., aged 72.

Benson.—On September 7, 1954, at Hampstead, London, N.W., Ernest George Dryden Benson, L.R.C.P.&S.Ed., L.R.F.P.S., D.P.H., late of Stanley, Co. Durham.

Blackburne.—On August 31, 1954, Alan John Blackburne, M.B., Ch.M., of Aston House, Bognor Regis, Sussex.

Blumer.—On August 29, 1954, at Staffordshire General Infirmary, Charles Eric Milnes Blumer, M.B., F.R.C.S.Ed., of Abbey Lands, Weston-on-Trent, Staffordshire.

Constantine.—On September 8, 1954, at Bradford, Yorks, Mary Cecilia Emsley Constantine, M.D., late of Karachi, Pakistan.

Deakin.—On September 4, 1954, at Truro Infirmary, Howard Vipond Deakin, M.D., of Byways, Carlyon Bay, St. Austell, Cornwall, aged 65.

Fry.—On September 1, 1954, Arthur Brownfield Fry, C.B., C.I.E., D.S.O., M.D., D.T.M.&H., Colonel, I.M.S., retired, aged 81.

Gilmour.—On August 29, 1954, Richard Withers Gilmour, M.B., B.S., M.R.C.P., of 20, Vincent Road, Stoke D'Abernon, Surrey, aged 84.

Hanna.—On August 31, 1954, at his home, Culderry House, Samarès, Jersey, C.I., John Ridgway Hanna, M.B., B.Ch., aged 53.

Hayward.—On September 4, 1954, at 11, King Edward's Road, Ruislip, Middlesex, Charles William Hayward, L.M.S.S.A.

Ness.—On September 7, 1954, at 19, Woodside Place, Glasgow, Robert Barclay Ness, M.B., C.M., F.R.F.P.S.

Norman.—On August 28, 1954, Newman Frederick Norman, M.R.C.S., L.R.C.P., of Westcliff-on-Sea, Essex.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Reliability of Mass Miniature Radiography

Q.—*How reliable is radiography in the detection of pulmonary neoplasm and pulmonary tuberculosis, and how does mass miniature radiography compare with full-size radiography for this purpose? How common are false positives in mass miniature radiography?*

A.—Many cases of pulmonary neoplasm cannot be detected by radiography in their early stages, and to a less extent the same is true of some cases of pulmonary tuberculosis. Nevertheless, in the great majority of cases radiological abnormality is present before any abnormality can be detected by other means, and often before symptoms occur, especially symptoms of sufficient severity for the patient to seek medical advice. Birkelo *et al.*[1] performed the classical comparison between various types of radiography for their efficiency in detecting pulmonary abnormalities. Their results showed that there is little to choose between miniature radiography and the full-size film for the detection of abnormalities. They further showed that any differences due to radiographic techniques are very small compared with the differences between two observers reading the same set of films, small or large, and small compared with the differences between the readings made by one observer on two separate occasions.

It is not quite clear what is meant by "false positives." A certain proportion of patients (2%–3%) will be recalled for full-size radiography who will be found to have no significant abnormality on the large film. "False positives" in the sense of further action than this will be no more frequent in mass miniature radiography than in standard radiography. Mass miniature radiography is only a sieve to select cases for study by other methods, and this question is closely connected with the factor of observer variability referred to above.

REFERENCE

[1] *J. Amer. med. Ass.*, 1947, **133**, 359.

Infective Hepatitis in Pregnancy

Q.—*If a member of the family of an expectant mother suffers from infective hepatitis, should any measures be taken to protect her against the risk of acquiring the infection? Will an attack of infective hepatitis make her more liable to toxaemia of pregnancy? Is gamma globulin advised?*

A.—Infective hepatitis can cause liver damage which varies in degree and duration, but this does not mean that during pregnancy it increases the risk of pre-eclampsia and eclampsia. A liver lesion is not the primary cause of these states. There is some evidence to show that the association of pregnancy with infective hepatitis *may* favour more extensive liver necrosis and that it may progress to acute yellow atrophy, especially in women suffering from dietetic deficiencies. Many authorities go so far as to say that *all* cases of acute yellow atrophy are primarily cases of infective hepatitis, although this all-embracing view would not be universally accepted. However, most women who suffer from infective hepatitis during pregnancy come to no serious harm. Thus, in a series of 91 cases reported from Scandinavia in 1951, only one woman died (of acute yellow atrophy); and with a much smaller experience the writer has not seen infective hepatitis in pregnant women give cause for real anxiety for the mother.

There is more danger to the foetus by way of abortion, intrauterine death, and premature labour, although here again the foetus is often unaffected. A significant association between malformation of the foetus and infective hepatitis has not been established.

By the time infective hepatitis is fully manifest and the diagnosis made, the most infectious phase is past, so the pregnant woman in question, if she is susceptible, is probably already infected. Considering this and bearing in mind that the risk to the pregnant woman is not proved to be materially greater than to any non-pregnant contact, it is doubtful whether a special case can be made out for using gamma globulin. The best means of protecting a pregnant woman from severe manifestations of the disease is to ensure that she has a diet which is rich in animal protein, carbohydrate, and vitamin-B complex.

Vitamin C for Surgical Patients

Q.—*Is there any justification for routine administration of vitamin C to surgical patients? If so, what is a suitable dose? Are there any contraindications?*

A.—There is abundant evidence, both from practical experience and from the laboratory, that an adequate supply of vitamin C is necessary for the healing of wounds. Furthermore, the surveys carried out by the Accessory Food Factors Committee of the Medical Research Council and by several independent investigators indicate clearly that the usual diet of a very large number of the population of this country does not supply sufficient vitamin C to ensure the rapid and sound healing of major wounds. The need for vitamin C in a particular patient may be assessed by giving ascorbic acid and determining its concentration in the urine, but for practical purposes it is better to assume that there is likely to be a deficiency and to give sufficient ascorbic acid to saturate the body before any major operation.

Patients who are apparently well nourished should be given 500 mg. of ascorbic acid daily for three days and then kept on a maintenance dose of 100 mg. daily throughout the period of operation and convalescence. These doses will have to be increased for patients suffering from malnutrition, from acute infections, and from carcinoma; if the carcinoma is of the stomach ascorbic acid should be given by injection, and the same applies, of course, to patients who are vomiting. There are no contraindications to giving sufficient vitamin C to maintain saturation of the body throughout the period of surgical treatment.

The Case for Ultraviolet Light

Q.—*Has treatment with ultraviolet light any therapeutic value other than its effect in assisting in the formation of vitamin D from ergosterol in the skin? The body protects itself by manufacturing a brown pigment in response to ultraviolet irradiation, so should not such therapy be regarded as in fact harmful?*

A.—Precise and detailed knowledge of the effect of ultraviolet light on the skin is lacking. The tonic effect of exposure may be partly due to the production of vitamin D in the skin; it may be partly psychological; it may, on the other hand, be due to effects of which we as yet know little.

For the most part ultraviolet light is now used for its local effect in various disorders of the skin. It has for many years been a valuable treatment in tuberculous lupus and it is not at all certain that antibiotic treatment has made local ultraviolet light unnecessary. Another principal use is in the treatment of psoriasis, particularly in conjunction with applications containing tar. Its value in acne vulgaris and alopecia areata is probably due to a non-specific effect in provoking a mild inflammatory change. It is also useful in helping to heal bedsores and indolent ulcers.

There is no reason to regard ultraviolet light as harmful simply because it stimulates pigment production. Some of the ultraviolet wavelengths which are biologically very active, and therefore potentially harmful, stimulate very little pigment production. The effect of pigmentation is to limit the penetration of ultraviolet light into the dermis, but it means that more is held up in the epidermis, thus exerting a greater biological activity in that layer.